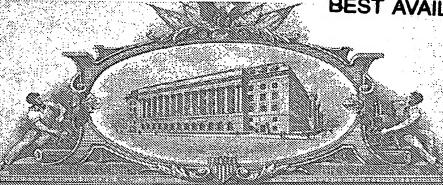
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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

November 22, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/458,026
FILING DATE: March 28, 2003
RELATED PCT APPLICATION NUMBER: PCT/US04/09510

Certified by



Jon W Dudas

Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the U.S. Patent and Trademark Office

Provisional Application For Patent Cover Sheet This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C. F. R. S.

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INVENTOR(S)												
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Denise Marie		BAKER		Poway, California		9 ≣						
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Robert W.		CHESNUT		Cardiff-by-the-Sea		.a.						
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Mark J.		NEWMAN		Carlsbad, Californ	ша	- 190						
Additional inventor's are being named on the separately numbered sheets attached hereto.												
TITLE OF THE INVENTION (500 Characters Maximum)												
CORRESPONDENCE ADDRESS												
Direct all correspondence to: Place Customer Number												
☑ Customer number 26111 → Bar Code Label here 26111												
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OR Company												
☐ Firm or I	STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.											
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An Extension Of Time Under 3 / C.F.R. § 1.136(a)(3) Application Data Sheet. See 37 CFR 1.76												
METHOD OF	PAYMENT OF F	LING FEES FOR THIS PRO	VISIONAL APP	LICATION FOR PATENT (check one)							
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		ene C. Carlson		Registration No. 47,473 (if appropriate)								
Telephone: 202-371-2600 Docket Number: 2060.0260000/EKS/HCC USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT												
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Robert Greene Steme Edward J. Kessler Jorge A. Goldstein David K.S. Cornwell Robert W. Exmond Tacy-Gene G. Durkin Michee A. Cimbala Michael B. Ray Robert E. Southi Eric K. Staffe Michael Q. Lee Michael Q. Lee Michael Q. Lee Steven R. Ludwig John M. Covert Linde E. Altom Robert C. Millonin Lawrence R. Bugalsky

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*Admitted only in Maryland
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*Admitted only in Texas
*Practice Limited to

March 28, 2003

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JC887 U.S. PTO 60/458026

Commissioner for Patents Washington, D.C. 20231

Box Provisional Application

Re:

U.S. Provisional Patent Application

Appl. No. To be assigned; Filed: March 28, 2003

For: Methods Of Identifying Optimal Variants Of Peptide Epitopes

Inventors: BAKER et al.

Our Ref: 2060.0260000/EKS/HCC

Sir:

The following documents are being submitted under 37 C.F.R. § 1.53(c) herewith for appropriate action by the U.S. Patent and Trademark Office:

- 1. PTO Fee Transmittal (Form PTO/SB/17);
- 2. U.S. Provisional Patent Application entitled:

Methods Of Identifying Optimal Variants Of Peptide Epitopes

and naming as inventors:

Denise Marie BAKER
Brian D. LIVINGSTON
Robert W. CHESNUT
Alessandro SETTE
Mark J. NEWMAN

the application consisting of:

a. A Provisional Application for Patent Cover Sheet;

Sterne, Kessler, Goldstein & Fox PLLC : 1100 New York Avenue, NW : Washington, DC 20005 : 202.371.2600 f 202.371.2540 : www.skgf.com

Commissioner for Patents March 28, 2003 Page 2

- b. an Application Data Sheet (37 C.F.R. § 1.76);
- c. A specification containing 457 total pages:
 - (i) 452 pages of description prior to any claims;
 - (ii) 4 pages of claims (30 claims); and
 - (iii) a one page abstract;
- d. 5 sheets of drawings: (Figures 1A-4); and
- 3. Authorization to Treat a Reply As Incorporating An Extension of Time Under 37 C.F.R. § 1.136(a)(3);
- 4. Form PTO-2038 Credit Card Payment Form in the amount of \$160.00 to cover the filing fee; and
- 5. Two (2) return postcards.

It is respectfully requested that, of the two attached postcards, one be stamped with the filing date of these documents and returned to our courier, and the other, prepaid postcard, be stamped with the filing date and returned as soon as possible.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson

Agent for Applicants

Registration No. 47,473

EKS/HCC/eaf Enclosures

SKGF_DC1:117771.1

Approved for use through 10/31/2002. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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Patent fees are subject to annual revision.		First Named Inventor			Denise Marie BAKER				
☐ Applicant claims small entity status. See 37 CFR 1.27	_ [Examiner Name To be assi			To be assigne	ed			
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This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retains benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.17. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the complete form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 26111

Fax One:: (202) 371-2540

APPLICATION INFORMATION

)

Title Line One:: Methods Of Indentifying Optimal Variants
Title Line Two:: Of Peptide Epitopes

Formal Drawings?:: No

Application Type:: Provisional Docket Number:: 2060.0260000 Secrecy Order in Parent Appl.?:: No

REPRESENTATIVE INFORMATION

Representative Customer Number:: 26111

Source:: PrintEFS Version 1.0.1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BAKER et al.

Appl. No. To be assigned

Filed: March 28, 2003

For: Methods Of Identifying Optimal

Variants Of Peptide Epitopes

Art Unit: To be assigned

Examiner: To be assigned

Atty. Docket: 2060.0260000/EKS/HCC

Authorization To Treat A Reply As Incorporating An Extension Of Time Under 37 C.F.R. § 1.136(a)(3)

Commissioner for Patents Washington, D.C. 20231

Sir:

The U.S. Patent and Trademark Office is hereby authorized to treat any concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extension of time fees to our Deposit Account No. 19-0036, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson Agent for Applicants Registration No. 47,473

Date: March 28, 2003

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(202) 371-2600

Attorney Docket No: 2060.026000 EPI 0141.20 US

METHODS OF IDENTIFYING OPTIMAL VARIANTS OF PEPTIDE EPITOPES

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Assignee:

Epimmune Inc.

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY-SPONSORED RESEARCH AND DEVELOPMENT

[0001] This invention was funded, in part, by the United States government under grants with the National Institutes of Health. The U.S. government has certain rights in this invention.

REFERENCE TO MICROFICHE APPENDIX/SEQUENCE LISTING/TABLE/COMPUTER PROGRAM LISTING APPENDIX (submitted on a compact disc and an incorporation-by-reference of the material on the compact disc)

[0002] Not applicable.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] This invention relates to the field of biology. In a particular embodiment, it relates to peptides, polynucleotides, and compositions useful to monitor or elicit an immune response to selected antigens, and methods of identifying such peptides and polynucleotides.

Related Art

- [0004] HLA class I molecules are expressed on the surface of almost all nucleated cells. Following intracellular processing of antigens, epitopes from the antigens are presented as a complex with the HLA class I molecules on the surface of such cells. CTL recognize the peptide-HLA class I complex, which then results in the destruction of the cell bearing the HLA-peptide complex directly by the CTL and/or via the activation of non-destructive mechanisms e.g., the production of interferon, that inhibit viral replication.
- [0005] Human Immunodeficiency Virus. Acquired immunodeficiency syndrome (AIDS) caused by infection with human immunodeficiency virus-1 (HIV-1) represents a major world health problem. Estimates indicate that about 16,000 people worldwide are infected with HIV each day.
- [0006] The development of anti-viral drugs has been a major advancement in reducing viral loads in IIIV infected patients. Highly active retroviral therapy (HAART) has been shown to reduce viremia to nearly undetectable levels. However, current drug therapies are not practicable as a long term solution to the HIV epidemic. HAART therapy is severely limited due to poor tolerance for the drugs and the emergence of drug-resistant virus. Moreover, replication competent HIV persists in the lymphoid tissue of patients who have responded to HAART, thus serving as a reservoir of virus. Lastly, current anti-retroviral drug therapies have little impact upon the global

epidemic: almost 90% of the world's HIV infected population resides within countries lacking financial resources for these drugs. Thus, a need exists for an efficacious vaccine to both prevent and treat HIV infection.

[0007] Virus-specific, human leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocytes (CTL) are known to play a major role in the prevention and clearance of virus infections in vivo (Oldstone et al., Nature 321:239, 1989; Jamieson et al., J. Virol. 61:3930, 1987; Yap et al, Nature 273:238, 1978; Lukacher et al., J. Exp. Med. 160:814, 1994; McMichael et al., N. Engl. J. Med. 309:13, 1983; Sethi et al., J. Gen. Virol. 64:443, 1983; Watari et al., J. Exp. Med. 165:459, 1987; Yasukawa et al., J. Immunol. 143:2051, 1989; Tigges et al., J. Virol. 66:1622, 1993; Reddenhase et al., J. Virol. 55:263, 1985; Quinnan et al., N. Engl. J. Med. 307:6, 1982).

While immune correlates of protective immunity against HIV infection are not well defined, there is a growing body of evidence that suggests CTL are important in controlling HIV infection. HIV-specific CTL responses can be detected early in infection and the appearance of the responses corresponds to the time in infection at which initial viremia is reduced (Pantaleo et al., Nature 370:463, 1994; Walker et al., Proc. Natl. Acad. Sci. 86:9514, 1989). In addition, HIV replication in infected lymphocytes can be inhibited by incubation with autologous CTL (see, e.g., Tsubota et al., J. Exp. Med. 169:1421, 1989). These data are supported by recent studies that indicate CTL are required for controlling viral replication in a SIV/rhesus animal model (Schmitz et al., Science 283:857, 1999), and additionally supported by studies that demonstrate that CTL exert selective pressure on HIV populations as evidenced by the eventual predominance of viruses with amino acid replacements in those regions of the virus to which CTL responses are directed (see, e.g., Borrow ct al., Nature Med. 3:205-211, 1997; Price et al., Proc. Nat. Acad. Sci. 94:12890-1895, 1997; Koenig et al., Nature Med. 1:330-336, 1995; and Haas et al., J. Immunol. 157:4212-4221, 1996).

[0009] Virus-specific T helper lymphocytes are also known to be critical for maintaining effective immunity in chronic viral infections. Historically, HTL responses were viewed as primarily supporting the expansion of specific CTL and B cell populations; however, more recent data indicate that HTL may directly contribute to the control of virus replication. For example, a decline in CD4⁺ T cells and a corresponding loss in HTL function characterize infection with HIV (Lane et al., New Engl. J. Med. 313:79, 1985). Furthermore, studies in HIV infected patients have also shown that there is an inverse relationship between virus-specific HTL responses and viral load, suggesting that HTL play a role in viremia (see, e.g., Rosenberg et al., Science 278:1447, 1997).

[0010] A fundamental challenge in the development of an efficacious HIV vaccine is the heterogeneity observed in HIV. The virus, like some other infectious agents including retroviruses, rapidly mutates during replication resulting in the generation of virus that can escape

anti-viral therapy and immune recognition (Borrow et al., Nature Med. 3:205, 1997). In addition, HIV can be classified into a variety of subtypes that exhibit significant sequence divergence (see, e.g., Lukashov et al., AIDS 12:S43, 1998). In view of the heterogeneous nature of HIV, and the heterogeneous immune response observed with HIV infection, induction of a multi-specific cellular immune response directed simultaneously against multiple HIV epitopes appears to be important for the development of an efficacious vaccine against HIV. There is a need to establish such vaccine embodiments which elicit immune responses of sufficient breadth and vigor to prevent and/or clear HIV infection.

- [0011] Hepatitis B Virus. Chronic infection by hepatitis B virus (HBV) affects at least 5% of the world's population and is a major cause of cirrhosis and hepatocellular carcinoma (Hoofnagle, J., N. Engl. J. Med. 323:337, 1990; Fields, B. and Knipe, D., In: Fields Virology 2:2137, 1990). The World Health Organization lists hepatitis B as a leading cause of death worldwide, close behind chronic pulmonary disease, and more prevalent than AIDS. Chronic HBV infection can range from an asymptomatic carrier state to continuous hepatocellular necrosis and inflammation, and can lead to hepatocellular carcinoma.
- [0012] The immune response to HBV is believed to play an important role in controlling hepatitis B infection. A variety of humoral and cellular responses to different regions of the HBV nucleocapsid core and surface antigens have been identified. T cell mediated immunity, particularly involving class I human leukocyte antigen-restricted cytotoxic T lymphocytes (CTL), is believed to be crucial in combatting established HBV infection.
- [0013] Several studies have emphasized the association between self-limiting acute hepatitis and multispecific CTL responses (Penna, A. et al., J. Exp. Med. 174:1565, 1991; Nayersina, R. et al., J. Immunol. 150:4659, 1993). Spontaneous and interferon-related clearance of chronic HBV infection is also associated with the resurgence of a vigorous CTL response (Guidotti, L. G. et al., Proc. Natl. Acad. Sci. USA 91:3764, 1994). In all such cases the CTL responses are polyclonal, and specific for multiple viral proteins including the HBV envelope, core and polymerase antigens. By contrast, in patients with chronic hepatitis, the CTL activity is usually absent or weak, and antigenically restricted.
- [0014] The crucial role of CTL in resolution of HBV infection has been further underscored by studies using HBV transgenic mice. Adoptive transfer of HBV-specific CTL into mice transgenic for the HBV genome resulted in suppression of virus

replication. This effect was primarily mediated by a non-lytic, lymphokine-based mechanism (Guidotti, L. G. et al., *Proc. Natl. Acad. Sci. USA* 91:3764, 1994; Guidotti, L. G., Guilhot, S., and Chisari, F. V. *J. Virol.* 68:1265, 1994; Guidotti, L. G. et al., *J. Virol.* 69:6158, 1995; Gilles, P. N., Fey, G., and Chisari, F. V., *J. Virol.* 66:3955, 1992).

- [0015] As is the case for HLA class I restricted responses, HLA class II restricted T cell responses are usually detected in patients with acute hepatitis, and are absent or weak in patients with chronic infection (Chisari, F. V. and Ferrari, C., Annu. Rev. Immunol. 13:29, 1995). HLA Class II responses are tied to activation of helper T cells (HTLs) Helper T lymphocytes, which recognize Class II HLA molecules, may directly contribute to the clearance of HBV infection through the secretion of cytokines which suppress viral replication (Franco, A. et al., J. Immunol. 159:2001, 1997). However, their primary role in disease resolution is believed to be mediated by inducing activation and expansion of virus-specific CTL and B cells.
- [0016] In view of the heterogeneous immune response observed with HBV infection, induction of a multi-specific cellular immune response directed simultaneously against multiple epitopes appears to be important for the development of an efficacious vaccine against HBV. There is a need to establish vaccine embodiments that elicit immune responses that correspond to responses seen in patients that clear HBV infection. Epitope-based vaccines appear useful.
- Hepatitis C Virus. Hepatitis C virus (HCV) infection is a global human health problem with approximately 150,000 new reported cases each year in the U.S. alone. HCV is a single stranded RNA virus, and is the etiological agent identified in most cases of non-A, non-B post-transfusion and post-transplant hepatitis, and is a common cause of acute sporadic hepatitis (Choo et al., Science 244:359, 1989; Kuo et al., Science 244:362, 1989; and Alter et al., in: Current Perspective in Hepatology, p. 83, 1989). It is estimated that more than 50% of patients infected with HCV become chronically infected and, of those, 20% develop cirrhosis of the liver within 20 years (Davis et al., New Engl. J. Med. 321:1501, 1989; Alter et al., in: Current Perspective in Hepatology, p. 83, 1989; Alter et al., New Engl. J. Med. 327:1899, 1992; and Dienstag, J. L. Gastroenterology 85:430, 1983). Moreover, the only therapy available for treatment of HCV infection is interferon-α. Most patients are unresponsive, however, and among the responders, there is a high recurrence rate within 6-12 months of cessation of treatment (Liang et al., J. Med. Virol.

40:69, 1993). Ribaviron, a guanosine analog with a broad spectrum activity against many RNA and DNA viruses, has been shown in clinical trials to be effective against chronic HCV infection when used in combination with interferon- α (see, e.g., Poynard et al., Lancet 352:1426-1432, 1998; Reichard et al., Lancet 351:83-87, 1998) However, the response rate is still well below 50%.

- lymphocytes (CTL) are known to play a major role in the prevention and clearance of virus infections in vivo (Oldstone et al., Nature 321:239, 1989; Jamieson et al., J. Virol. 61:3930, 1987; Yap et al, Nature 273:238, 1978; Lukacher et al., J. Exp. Med. 160:814, 1994; McMichael et al., N. Engl. J. Med. 309:13, 1983; Sethi et al., J. Gen. Virol. 64:443, 1983; Watari et al., J. Exp. Med. 165:459, 1987; Yasukawa et al., J. Immunol. 143:2051, 1989; Tigges et al., J. Virol. 66:1622, 1993; Reddenhase et al., J. Virol. 55:263, 1985; Quinnan et al., N. Engl. J. Med. 307:6, 1982).
- [0019] In view of the heterogeneous immune response observed with HCV infection, induction of a multi-specific cellular immune response directed simultaneously against multiple HCV epitopes appears to be important for the development of an efficacious vaccine against HCV. There is a need, however, to establish vaccine embodiments that elicit immune responses that correspond to responses seen in patients that clear HCV infection.
- [0020] Human Papillomavirus. Human papillomavirus (HPV) is a member of the papillomaviridae, a group of small DNA viruses that infect a variety of higher vertebrates. More than 80 types of HPVs have been identified. Of these, more than 30 can infect the genital tract. Some types, generally types 6 and 11, may cause genital warts, which are typically benign and rarely develop into cancer. Other strains of HPV, "cancer-associated", or "high-risk" types, can more frequently lead to the development of cancer. The primary mode of transmission of these strains of HPV is through sexual contact.
- [0021] The main manifestations of the genital warts are cauliflower-like condylomata acuminata that usually involve moist surfaces; keratotic and smooth papular warts, usually on dry surfaces; and subclinical "flat" warts, which are found on any mucosal or cutaneous surface (Handsfield, H., Am. J. Med. 102(5A):16-20, 1997). These warts are typically benign but are a source of inter-individual spread of the virus (Ponten, J. & Guo, Z., Cancer Surv. 32:201-29, 1998). At least three HPV strains associated with genital warts

have been identified: type 6a (see, e.g., Hofmann, K.J., et al., Virology 209(2):506-518, 1995), type 6b (see, e.g., Hofmann et al., supra) and type 11 (see, e.g., Dartmann, K. et al., Virology 151(1):124-130, 1986).

- Cancer-associated HPVs have been linked with cancer in both men and women; they include, but are not limited to, HPV-16, HPV-18, HPV-31, HPV-45, HPV-33 and HPV-56. Other HPV strains, including types 6 and 11 as well as others, e.g., HPV-5 and HPV-8, are less frequently associated with cancer. The high risk types are typically associated with the development of cervical carcinoma and premalignant lesions of the cervix in women, but are also associated with similar malignant and premalignant lesions at other anatomic sites within the lower genital or anogenital tract. These lesions include neoplasia of the vagina, vulva, perineum, the penis, and the anus. HPV infection has also been associated with respiratory tract papillomas, and rarely, cancer, as well as abnormal growth or neoplasia in other epithelial tissues. See, e.g. VIROLOGY, 2ND ED, Fields et al., Eds. Raven Press, New York, 1990, Chapters 58 and 59, for a review of HPV association with cancer.
- The HPV genome consists of three functional regions, the early region, the late region, and the "long control region". The early region gene products control viral replication, transcription and cellular transformation. They include the HPV E1 and E2 proteins, which play a role in HPV DNA replication, and the E6 and E7 oncoproteins, which are involved in the control of cellular proliferation. The late region include the genes that encode the structural proteins L1 and L2, which are the major and minor capsid proteins, respectively. The "long control region" contains such sequences as enhancer and promoter regulatory regions.
- [0024] HPV expresses different proteins at different stages of the infection, for example early, as well as late, proteins. Even in latent infections, however, early proteins are often expressed and are therefore useful targets for vaccine-based therapies. For example, high-grade dysplasia and cervical squamous cell carcinoma continue to express E6 and E7, which therefore can be targeted to treat disease at both early and late stages of infection.
- [0025] Treatment for HPV infection is often unsatisfactory because of persistence of virus after treatment and recurrence of clinically apparent disease is common. The treatment may require frequent visits to clinics and is not directed at elimination of the virus but at clearing warts. Because of persistence of virus after treatment, recurrence of clinically apparent disease is common.

- [0026] Thus, a need exists for an efficacious vaccine to both prevent and treat HPV infection and to treat cancer that is associated with HPV infection. Effective HPV vaccines would be a significant advance in the control of sexually transmissable infections and could also protect against clinical disease, particularly cancers such as cervical cancer. (see, e.g., Rowen, P. & Lacey, C., Dermatologic Clinics 16(4):835-838, 1998).
- lymphocytes (CTL) are known to play a major role in the prevention and clearance of virus infections in vivo (Oldstone et al., Nature 321:239, 1989; Jamieson et al., J. Virol. 61:3930, 1987; Yap et al, Nature 273:238, 1978; Lukacher et al., J. Exp. Med. 160:814, 1994; McMichael et al., N. Engl. J. Med. 309:13, 1983; Sethi et al., J. Gen. Virol. 64:443, 1983; Watari et al., J. Exp. Med. 165:459, 1987; Yasukawa et al., J. Immunol. 143:2051, 1989; Tigges et al., J. Virol. 66:1622, 1993; Reddenhase et al., J. Virol. 55:263, 1985; Quinnan et al., N. Engl. J. Med. 307:6, 1982).
- Virus-specific T helper lymphocytes are also known to be critical for maintaining effective immunity in chronic viral infections. Historically, HTL responses were viewed as primarily supporting the expansion of specific CTL and B cell populations; however, more recent data indicate that HTL may directly contribute to the control of virus replication. For example, a decline in CD4⁺ T cells and a corresponding loss in HTL function characterize infection with HIV (Lane et al., New Engl. J. Med. 313:79, 1985). Furthermore, studies in HIV infected patients have also shown that there is an inverse relationship between virus-specific HTL responses and viral load, suggesting that HTL plays a role in viremia (see, e.g., Rosenberg et al., Science 278:1447, 1997).
- [0029] The development of vaccines with prophylactic and therapeutic efficacy against HPV is ongoing. Early vaccine development was hampered by the inability to culture HPV. With the introduction of cloning techniques and protein expression, however, some attempts have been made to stimulate humoral and CTL response to HPV (See, e.g., Rowen, P. & Lacey, C., Dermatologic Clinics 16(4):835-838 (1998)). Studies to date, however, have been inconclusive.
- [0030] Activation of T helper cells and cytotoxic lymphocytes (CTLs) in the development of vaccines has also been analyzed. Lehtinen, M., et al. for instance, has shown that some peptides from the E2 protein of HPV type 16 activate T helper cells and CTLs (Biochem. Biophys. Res. Commun. 209(2):541-6 (1995). Similarly, Tarpey et al, has shown that some peptides from HPV type 11 E7 protein can stimulate human HPV-specific CTLs in

vitro (Immunology 81:222-227 (1994)) and Borysiewicz et al. have reported a recombinant vaccinia virus expressing HPV 16 and HPV 17 E6 and E7 that stimulated CTL responses in at least one patient (Lancet 347:1347-1357, 1996).

- [0031] Plasmodium falciparum and Malaria. Malaria, which is caused by infection with the parasite Plasmodium falciparum (PF), represents a major world health problem. Approximately 500 million people in the world are at risk from the disease, with approximately 200 million people actually harboring the parasites. An estimated 1 to 2 million deaths occur each year due to malaria. (Miller et al., Science 234:1349, 1986).
- [0032] Fatal outcomes are not confined to first infections, and constant exposure is apparently a prerequisite for maintaining immunity. Naturally acquired sterile immunity is rare, if it exists at all. Accordingly, major efforts to develop an efficacious malaria vaccine have been undertaken.
- Human volunteers injected with irradiated PF sporozoites are resistant to subsequent sporozoite challenges, which demonstrates that development of a malaria vaccine is indeed immunologically feasible. Furthermore, these immune individuals developed a vigorous response, including antibodies, and cytotoxic T lymphocyte (CTL) and helper T lymphocyte (HTL) components, directed against multiple antigens. Reproducing the breadth and multiplicity of this response in a vaccine, however, is a task of large proportions. The epitope approach, as described herein, may represent a solution to this challenge, in that it allows the incorporation of various antibody, CTL and HTL epitopes, from various proteins, in a single vaccine composition.
- [0034] Anti-sporozoite antibodies are by themselves, in general, not completely efficacious in clearing the infection (Egan et al., Science 236:453, 1987). However, high concentrations of antibodies directed against the repeated region of the major B cell antigen of the sporozoite/circumsporozoite protein (CSP) have been shown to prevent liver cell infection in certain experimental models (Egan et al., Science 236:453, 1987; Potocnjak, P. et al., Science 207:71, 1980). The present inventors have shown that constructs encompassing CSP-repeat B cell epitopes and the optimized helper epitope PADRETM (San Diego, CA) are highly immunogenic, and can protect in vitro against sporozoite invasion in both mouse and human liver cells, and protect mice in vivo against live sporozoite challenge (Franke et al., Vaccine 17:1201-1205, 1999)

- [0035] PF-specific CD4⁺ T cells also have a role in malarial immunity beyond providing help for B cell and CTL responses. Experiments by Renia et al. (Renia, et al., Proc. Natl. Acad. Sci. USA 88:7963, 1991) demonstrated that HTLs directed against the Plasmodium yoelli CS protein could in fact adoptivley transfer protection against malaria.
- [0036] Considerable data implicate CTLs in protection against pre-erythrocytic-stage malaria. CD8⁺ CTLs can eliminate *Plasmodium berghei* or *Plasmodium yoelii*-infected mouse hepatocytes from in vitro culture in a major histocompatibility complex (MHC)-restricted and antigen-restricted manner (Hoffman *et al.*, *Science* 244:1078-1081, 1989; Weiss *et al.*, J. *Exp. Med.* 171:763-773, 1990). Further, it has also been shown that the immunity that developed in mice vaccinated with irradiated sporozoites is also dependent upon the present of CD8+ T cells. These T cells accumulate in inflammatory liver infiltrates subsequent to challenge. Passive transfer of circumsporozoite (CSP)-specific CTL clones as long as three hours after inoculation of sporozoites (*i.e.*, after the parasites have left the bloodstream and infected liver cells) were capable of protecting animals against infection (Romero *et al.*, *Nature* 341:323, 1989).
- [0037] It is notable that CTL-restricted responses directed against a single antigen are insufficient to protect mice with different MHC alleles, and a combination of multiple antigens was required even to protect mice from the most common laboratory strains of *Plasmodium*. These data indicate that a combination of epitopes form several antigens is necessary to elicit a protective CTL response.
- Indirect evidence that CTLs are important in protective immunity against Pf in humans has also accumulated. It has been reported that cytotoxic CD8⁺ T cells can be identified in humans immunized with PF sporozoites (Moreno, et al., Int. Immunol. 3:997, 1991). Further, humans immunized with irradiated sporozoites or naturally exposed to malaria can generate a CTL response to the pre-erythrocytic-stage antigens, CSP, sporozoite surface protein 2 (SSP2), liver-stage antigen-1 (LSA-1), and exported protein-1 (Exp-1) (see, e.g. Malik et al., Proc. Natl. Acad. Sci. USA 88, 3300-3304, 1991; Doolan et al., Int. Immunol. 3:511-516, 1991; Hill et al., Nature 360:434-439, 1992). Additionally, there is evidence that the polymorphism within the CSP may be the result of selection by CTLs of parasites that express variant forms (MCutchan and Water, Immunol. Lett. 25:23-26, 1990). This is based on the observation that the variation is nonsynonymous at the nucleotide level, thereby indicating selective pressure at the protein level. The polymorphism primarily maps to identified CTL and T helper epitopes (Doolan et al., Int.

Immunol. 5:27-46, 1993); and CTL responses to some of the parasite variants do not cross-react (Hill et al., supra). Finally, the MHC class I human leukocyte antigen (HLA)-Bw53 has been associated with resistance to severe malaria in The Gambia, and CTLs to a conserved epitope restricted by the HLA-Bw53 allele have been identified on P. falciparum LSA-1 (Hill et al., Nature 352:595-600, 1991; Hill et al., Nature 340:434-439, 1992). Since HLA-Bw53 is found in 15%-40% of the population of sub-Saharan Africa but in less than 1% of Caucasians and Asians, these data suggest evolutionary selection on the basis of protection against severe malaria.

- [0039] Thus, antibody, and both HLA class I and class II restricted responses directed against multiple sporozoite antigens appear to be involved in generating protective immunity to malaria. Furthermore, several important antigenic epitopes against which humoral and cellular immunity is focused have already been exactly delineated.
- [0040] In view of the heterogeneous immune response observed with PF infection, induction of a multi-specific cellular immune response directed simultaneously against multiple PF epitopes appears to be important for the development of an efficacious vaccine against PF. There is a need, however, to establish vaccine embodiments that elicit immune responses that correspond to responses seen in patients that clear PF infection.
- [0041] Epitope-Based Vaccines. The use of epitope-based vaccines has several advantages over current vaccines. The epitopes for inclusion in such a vaccine are to be selected from conserved regions of viral or tumor-associated antigens, in order to reduce the likelihood of escape mutants. The advantage of an epitope-based approach over the use of whole antigens is that there is evidence that the immune response to whole antigens is directed largely toward variable regions of the antigen, allowing for immune escape due to mutations. Furthermore, immunosuppressive epitopes that may be present in whole antigens can be avoided with the use of epitope-based vaccines.
- [0042] Additionally, with an epitope-based vaccine approach, there is an ability to combine selected epitopes (CTL and HTL) and additionally to modify the composition of the epitopes, achieving, for example, enhanced immunogenicity. Accordingly, the immune response can be modulated, as appropriate, for the target disease. Similar engineering of the response is not possible with traditional approaches.

- [0043] Another major benefit of epitope-based immune-stimulating vaccines is their safety. The possible pathological side effects caused by infectious agents or whole protein antigens, which might have their own intrinsic biological activity, is eliminated.
- [0044] An epitope-based vaccine also provides the ability to direct and focus an immune response to multiple selected antigens from the same pathogen. Thus, patient-by-patient variability in the immune response to a particular pathogen may be alleviated by inclusion of epitopes from multiple antigens from that pathogen in a vaccine composition. A "pathogen" may be an infectious agent or a tumor associated molecule.
- epitope-based immunotherapeutics has been the extreme polymorphism of HI.A molecules. In the past, effective non-genetically biased coverage of a population has been a task of considerable complexity; such coverage has required that epitopes be used specific for HLA molecules corresponding to each individual HLA allele. Therefore, impractically large numbers of epitopes would been required in order to cover ethnically diverse populations. Recently, methods have been developed that allow the identification of epitopes that bind multiple HLA molecules. Therefore, epitope-based vaccines can be designed that contain epitopes which, either individually or in combination, bind a greater number of HLA molecules. The resulting epitope-based vaccines have a greater breadth of population coverage across one or more continents and even worldwide.
- [0046] Variation in Epitopes of Infectious Agents. A challenge in the development of effective vaccines against infectious agents such as hepatitis B virus (HBV) (47, 60) hepatitis C virus (HCV) (61-63), human papilloma virus (HPV) (64, 65) Plasmodium falciparum (66), and human immunodeficiency virus (HIV-1) is the protein sequence variation associated with different isolates. This variation is the result of gene sequence mutations. When such mutations occur in regions encoding epitopes recognized by cytotoxic T-lymphocytes (CTL), they provide a mechanism for escape of the agent from immune system control.
- [0047] HIV-1 represents an infectious agent with an especially high frequency of sequence variation. The sequence variation associated with HIV-1 proteins from related isolates, members of the same clades or types, as well as unrelated isolates, is well documented (1). Viral escape from CTL induced as the result of natural infection or vaccines was documented in nonhuman primate models where the mechanism behind this

escape was mutation of the primary anchor residues in dominant CTL epitopes (5-9). Viral escape from HIV-specific CTL has also been strongly implied by data obtained from HIV-1 infected individuals whose disease status change, including the transition from acute to chronic infection (10, 11), loss of stable control of viral replication and subsequent progression to AIDS (4, 12) or mother-to-child transmission (13). Thus, HIV-1 genetic and protein sequence variation represent a significant challenge to immune system-based control of viral replication, both within infected individuals and within populations.

- [0048] While the public health need for a vaccine against HIV-1 is well recognized and accepted, the genetic variation of HIV-1 isolates represents a highly significant obstacle (1, 14-16). Several strategies have been proposed, some of which include:
 - (1) Designing vaccines on HIV-1 types prevalent within small, well defined populations or geographical regions, such as individual countries or regions, and producing multiple different vaccines for exclusive use within these countries or regions (16).
 - (2) Use of HIV-1 ancestral or consensus sequences based on HIV types present in larger target populations, such as groups of neighboring countries or continents (15, 17-19).
 - (3) Incorporation of viral gene products obtained from multiple different virus isolates, representing diversely different types or clades, into a single 'multi-valent' vaccine.
- Related vaccine design concepts that incorporate many of the advantages associated with the approaches described above are the use of highly conserved regions or epitopes derived from these regions as the basis of the vaccine. The logic behind this approach is that conserved regions of the viral genome are those that have been maintained through the evolution of HIV-1 because changes impact gene product function and general viral fitness. This theory is consistent with analyses of HIV-1 protein sequence data which demonstrated that CTL epitopes are concentrated in conserved regions and that regions devoid of CTL epitopes are the most variable (20). Additional support comes from published reports describing CTL responses, induced as the result of

natural infection or vaccination, that recognize viral proteins or epitopes common to viral isolates from diverse types or clades (21-26). Broad function CTL responses are also known to be correlated with slower progression to AIDS, at least for certain carefully studied populations (27, 28). Despite these reports and the clustering of CTL epitopes in conserved regions of HIV-1 gene products, amino acid sequence variation of analogous regions and epitopes from different viral isolates, both within the same type or clade and from different types, remains significant. There are currently no rules guiding the selection of conserved regions of CTL epitopes for use in vaccines other than the use of amino acid sequence identity (29).

[0050] A clear understanding of how CTL recognize pathogen infected cells has emerged over the past decade. It is now well established that small fragments of pathogen-derived proteins are generated, defined as peptide epitopes generally 8-11 amino acids in length, which bind to HLA-A, -B, or -C (human Class I Major Histocompatability Molecules) molecules expressed on the cell surface. Sequencing of naturally processed peptides bound to HLA molecules provided a means to identify the amino acid residues required for allele-specific epitope-peptide binding (30-32). Data obtained from X-ray crystallographic analysis of HLA-epitope peptide complexes, allowed for the identification and structural characterization of 'binding pockets' within the peptide binding cleft of HLA molecules. More refined epitope anchor motif definitions were then developed using data obtained from in vitro peptide-MHC binding assays. It is now well known that the main anchor residues typically occur at position 2 and the carboxyl terminus of peptides 8-11 amino acids in length, thus positions 8, 9, 10 or 11 (33-40). The definition of epitope peptide binding anchor motifs is the key to most, if not all, epitope prediction methods.

Initial CTL epitope identification methods were developed using common HLA alleles, such as HLA-A2.1. Motifs defined using different HLA molecules were found to be similar and this lead to the definition of HLA supertype families (41). The biological effect of this supertype relationship was first demonstrated for HIV-1 epitopes in a study where the HLA-A3 and -A11 epitope peptide binding patterns repertoires were demonstrated to be overlapping, not only with each other but also with HLA-A31, -A33 and -A*6801 (42). This binding specificity was defined as the HLA-A3 supertype. A significant overlap in peptide binding patterns was also demonstrated amongst several serologically distant HLA-B alleles (43, 44), and multiple HLA-A2 alleles (45, 46),

resulting in the definition of the HLA-B7 and HLA-A2 supertype families. Recognition of epitopes by CTL in a supertype manner has since been demonstrated to occur naturally in infectious diseases and cancer (47-53).

[0052] While only two positions within CTL epitopes are typically characterized as the primary binding anchor positions, the amino acids that can serve as the anchor residues are more variable. The preferred and tolerated amino acids that can serve as anchor residues for the HLA-A2, -A3 and -B7 supertype families of epitopes are listed in Table 1. It is possible for analogous IIIV-1 epitope peptides derived from different isolates, which differ with respect to the amino acids used as anchor residues, to bind to HLA molecules similarly. This type of variation can be as conserved since it is likely that CTL produced against one epitope would recognize the related epitope. Thus, variation limited to changes in anchor residues that result in sufficient epitope peptide binding to HLA molecules does not result in immune escape from CTL. Epitopes that contain this type of variation can be identified using the appropriately designed motif search algorithms.

The TCR of CTL has been reported to be somewhat flexible or promiscuous with respect to recognition of epitope peptides bound to HLA molecules. For HIV-1, this flexibility was demonstrated as CTL recognition of related, but slightly variable, epitopes by single clones of CTL produced following natural infection (54, 55). Similar flexibility of CTL epitope recognition was demonstrated using rhesus macaques and natural infection with SIV or immunization (56, 57). This observation is not unique to HIV-1 and SIV but rather the TCR appears to have evolved to allow promiscuous recognition of peptide epitope bound to MHC molecules (58).

[0054] Selective replacement of certain amino acids in CTL epitope peptides, amino acids thought to represent TCR contact points, is not only tolerated but can increase the recognition of the epitopes by CTL clones (59). The types of amino acid substitutions that can be incorporated, typically amino acids that are similar in chemical properties are best tolerated, and their positions, independent of primary anchor positions, within a selected number of CTL epitopes from tumor associated antigens were also defined.

[0055] For HIV-1 and other infectious agents, reproducible methods for predicting the CTL recognition of related variant epitopes that occur amongst isolates have not been developed. Nor have methods for identifying CTL epitopes that are most likely to induce broadly functional responses when used in vaccine. Thus, there exists a need to develop

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such methods to overcome the challenge associated with protein sequence variation in HIV and other infectious agents.

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SUMMARY OF THE INVENTION

- [0056] The present invention is directed to methods for selecting a variant of a peptide epitope which induces a CTL response against another variant(s) of the peptide epitope, by determining whether the variant comprises only conserved residues, as defined herein, at non-anchor positions in comparison to the other variant(s).
- In some embodiments, antigen sequences from a population of an infectious agent, said antigens comprising variants of a peptide epitope, are optionally aligned (manually or by computer) along their length, preferably their full length. Variant(s) of a peptide epitope (preferably naturally occurring variants), each 8-11 amino acids in length and comprising the same MHC class I supermotif or motif, are identified manually or with the aid of a computer. In some embodiments, a variant is optionally chosen which comprises preferred anchor residues of said motif and/or which occurs with high frequency within the population of variants. In other embodiments, a variant is randomly chosen. The randomly or otherwise chosen variant is compared to from one to all the remaining variant(s) to determine whether it comprises only conserved residues in the non-anchor positions relative to from one to all the remaining variant(s).
- [0058] The present invention is also directed to variants identified by the methods above; peptides comprising such variants; nucleic acids encoding such variants and peptides; cells comprising such variants, and/or peptides, and/or nucleic acids; compositions comprising such variants, and/or peptides, and/or nucleic acids, and/or cells; as well as therapeutic and diagnostic methods for using such variants, peptides, nucleic acids, cells, and compositions.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

- [0059] FIGS. 1A-1E. Recognition of variant peptides by CTL generated against a single epitope. Variant peptides were identified from 167 HIV strains for 5 HIV epitopes, 3 HLA-A2 restricted (Env 134, A, Gag 386, B, and Vpr 62, C) and 2 HLA-A11 restricted (Pol 98, D, and Env 47, E). These are listed according to their relationship to a previously determined parent (P) into single anchor substitutions (A), single non-anchor substitutions (NA) or multiple substitutions (M). Binding of each variant peptide is also shown. The number of viral sequences containing each variant peptide is shown in the column labeled # Isolates, and is reported for the total sequences, Clade B sequences (B), and Clade C sequences (C). Finally, the ability of CTL primed against the parent peptide to recognize the variant peptides is shown in the bar graphs.
- [0060] FIGS. 2A-2C. Characterization of the peptide-specific T cell lines. A. FACS analysis of the TCRs expressed by peptide -stimulated cells after 0, 1, and 5 peptide stimulations, using a panel of commercially available mAb for mouse TCR 2-14. B-C. Peptide affinity. Parent and variant peptides were titrated against CTL that had been stimulated 5 times with the parent peptide.
- [0061] FIGS. 2A-2B. Recognition of a panel of variant peptides by PBL from an HIV-infected individual.
- [0062] FIG 4. Prediction of immunological conservation. Gag 271 variants and their binding are shown, along with the number of isolates that express each variant. Immunological recognition was predicted for each variant based on two different choices in the immunizing peptide. On the right, the immunogenicity for each variant is shown.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

- [0063] The invention can be better understood with reference to the following definitions:
- [0064] An "antigen" refers to a polypeptide encoded by the genome of an infectious agent, or other another source, but preferably an infectious agent in the present invention.

Examples of HIV antigens include Env, Gag, Nef, Pol, Tat, Rev, Vif, Vpr, Vpu, p17, p24, p2, p7, p1, p6, Protease, RT, Integrase, and gp160 (preferably Env, Gag, Nef, Pol, Tat, Rev, Vif, Vpr, Vpu). Examples of HBV antigens include Core, Env, and Pol. Examples of HCV antigens include Core, E1, E2, Ns1, Ns2, Ns3, Ns4, and Ns5. Examples of HPV antigens include E1, E2, E3, E4, E5, E6, E7, L1, and L2. Examples of *Plasmodium falciparum* antigens include CSP, SSP2, Exp1, and LSA1.

[0065]

Throughout this disclosure, "binding data" results are often expressed in terms of "IC₅₀'s." IC₅₀ is the concentration of peptide in a binding assay at which 50% inhibition of binding of a reference peptide is observed. Given the conditions in which the assays are run (*i.e.*, limiting HLA proteins and labeled peptide concentrations), these values approximate K_D values. Assays for determining binding are described in detail, *e.g.*, in PCT publications WO 94/20127 and WO 94/03205, and other publications such Sidney *et al.*, Current Protocols in Immunology 18.3.1 (1998); Sidney, *et al.*, J. Immunol. 154:247 (1995); and Sette, *et al.*, Mol. Immunol. 31:813 (1994). It should be noted that IC₅₀ values can change, often dramatically, if the assay conditions are varied, and depending on the particular reagents used (*e.g.*, HLA preparation, *etc.*). For example, excessive concentrations of HLA molecules will increase the apparent measured IC₅₀ of a given ligand.

[0066]

Alternatively, binding is expressed relative to a reference peptide. Although as a particular assay becomes more, or less, sensitive, the IC_{50} 's of the peptides tested may change somewhat, the binding relative to the reference peptide will not significantly change. For example, in an assay run under conditions such that the IC_{50} of the reference peptide increases 10-fold, the IC_{50} values of the test peptides will also shift approximately 10-fold. Therefore, to avoid ambiguities, the assessment of whether a peptide is a good (i.e. high), intermediate, weak, or negative binder is generally based on its IC_{50} , relative to the IC_{50} of a standard peptide. The Tables included in this application present binding data in a preferred biologically relevant form of IC_{50} nM.

[0067]

Binding may also be determined using other assay systems including those using: live cells (e.g., Ceppellini et al., Nature 339:392 (1989); Christnick et al., Nature 352:67 (1991); Busch et al., Int. Immunol. 2:443 (1990); Hill et al., J. Immunol. 147:189 (1991); del Guercio et al., J. Immunol. 154:685 (1995)), cell free systems using detergent lysates (e.g., Cerundolo et al., J. Immunol. 21:2069 (1991)), immobilized purified MHC (e.g., Hill et al., J. Immunol. 152, 2890 (1994); Marshall et al., J. Immunol. 152:4946 (1994)), ELISA systems (e.g., Reay et al., EMBO J. 11:2829 (1992)), surface plasmon resonance (e.g., Khilko et al., J. Biol. Chem. 268:15425 (1993)); high flux soluble phase assays (Hammer et al., J. Exp. Med. 180:2353 (1994)), and measurement of class I MHC stabilization or assembly (e.g., Ljunggren et al., Nature 346:476 (1990);

Schumacher et al., Cell 62:563 (1990); Townsend et al., Cell 62:285 (1990); Parker et al., J. Immunol. 149:1896 (1992)).

- [0068] As used herein, "high affinity" with respect to HLA class I molecules is defined as binding with an IC₅₀ or K_D value, of 50 nM or less, "intermediate affinity" is binding with an IC₅₀ or K_D value of between 50 and about 500 nM, weak affinity is binding with an IC₅₀ or K_D value of between about 500 and about 5000 nM. "High affinity" with repect to binding to HLA class II molecules is defined as binding with an IC₅₀ or K_D value of 100 nM or less; "intermediate affinity" is binding with an IC₅₀ or K_D value of between about 100 and about 1000 nM.
- [0069] A "computer" or "computer system" generally includes: a processor and related computer programs; at least one information storage/retrieval apparatus such as a hard drive, a disk drive or a tape drive; at least one input apparatus such as a keyboard, a mouse, a touch screen, or a microphone; and display structure, such as a screen or a printer. Additionally, the computer may include a communication channel in communication with a network. Such a computer may include more or less than what is listed above.
- [0070] "Cross-reactive binding" indicates that a peptide is bound by more than one HLA molecule; a synonym is degenerate binding.
- [0071] A "cryptic epitope" elicits a response by immunization with an isolated peptide, but the response is not cross-reactive *in vitro* when intact whole protein, which comprises the epitope, is used as an antigen.
- [0072] The term "derived" when used to discuss an epitope is a synonym for "prepared." A derived epitope can be isolated from a natural source, or it can be synthesized in accordance with standard protocols in the art. Synthetic epitopes can comprise artificial amino acids "amino acid mimetics," such as D isomers of natural occurring L amino acids or non-natural amino acids such as cyclohexylalanine. A derived/prepared epitope can be an analog of a native epitope.
- [0073] A "diluent" includes sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred diluent for pharmaceutical compositions. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as diluents, particularly for injectable solutions.
- [0074] A "dominant epitope" is an epitope that induces an immune response upon immunization with a whole native antigen (see, e.g., Sercarz, et al., Annu. Rev. Immunol. 11:729-766, 1993). Such a response is cross-reactive in vitro with an isolated peptide epitope.
- [0075] An "epitope" is the collective features of a molecule, such as primary, secondary and tertiary peptide structure, and charge, that together form a site recognized by an immunoglobulin, T cell receptor or HLA molecule. Alternatively, an epitope can be defined as a set of amino acid residues which is involved in recognition by a particular immunoglobulin, or in the context of T

cells, those residues necessary for recognition by T cell receptor proteins and/or Major Histocompatibility Complex (MHC) receptors. Epitopes are present in nature, and can be isolated, purified or otherwise prepared/derived by humans. For example, epitopes can be prepared by isolation from a natural source, or they can be synthesized in accordance with standard protocols in the art. Synthetic epitopes can comprise artificial amino acids, "amino acid mimetics," such as D isomers of naturally-occurring L amino acids or non-naturally-occurring amino acids such as cyclohexylalanine. Throughout this disclosure, epitopes may be referred to in some cases as peptides. The variants of the invention are set forth in Tables 6-9 and Figures 1A-4.

[0076]

It is to be appreciated that proteins or peptides that comprise a variant of the invention as well as additional amino acid(s) are still within the bounds of the invention. In certain embodiments, the peptide comprises a fragment of an antigen. A "fragment of an antigen" or "antigenic fragment" or simply "fragment" is a portion of an antigen which has 100% identity with a wild type antigen or naturally-ocurring variant thereof. The fragment may or may not comprise an epitope of the invention. The fragment may be less than or equal to 600 amino acids, less than or equal to 500 amino acids, less than or equal to 400 amino acids, less than or equal to 250 amino acids, less than or equal to 100 amino acids, less than or equal to 85 amino acids, less than or equal to 75 amino acids, less than or equal to 65 amino acids, or less than or equal to 50 amino acids in length. In certain embodiments, a fragment is e.g., less than 101 or less than 51 amino acids in length, in any increment down to 5 amino acids in length. For example, the fragment may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length.

[0077]

In certain embodiments, there is a limitation on the length of a peptide of the invention. The embodiment that is length-limited occurs when the protein/peptide comprising an epitope of the invention comprises a region (i.e., a contiguous series of amino acids) having 100% identity with a native sequence. In order to avoid the definition of epitope from reading, e.g., on whole natural molecules, there is a limitation on the length of any region that has 100% identity with a native peptide sequence. Thus, for a peptide comprising an epitope of the invention and a region with 100% identity with a native peptide sequence, the region with 100% identity to a native sequence generally has a length of: less than or equal to 600 amino acids, often less than or equal to 500 amino acids, often less than or equal to 400 amino acids, often less than or equal to 250 amino acids, often less than or equal to 100 amino acids, often less than or equal to 85 amino acids, often less than or equal to 75 amino acids, often less than or equal to 65 amino acids, and often less than or equal to 50 amino acids. In certain embodiments, an "epitope" of the invention

is comprised by a peptide having a region with less than 51 amino acids that has 100% identity to a native peptide sequence, in any increment down to 5 amino acids.

- [0078] Accordingly, peptide or protein sequences longer than 600 amino acids are within the scope of the invention, so long as they do not comprise any contiguous sequence of more than 600 amino acids that have 100% identity with a native peptide sequence. For any peptide that has five contiguous residues or less that correspond to a native sequence, there is no limitation on the maximal length of that peptide in order to fall within the scope of the invention. It is presently preferred that a peptide of the invention (e.g., a peptide comprising an epitope of the invention) be less than 600 residues long in any increment down to eight amino acid residues.
- [0079] A peptide epitope occurring with "high frequency" is one that occurs in at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the infectious agents in a population. A "high frequency" peptide epitope is one of the more common in a population, preferably the first most common, second most common, third most common, or fourth most common in a population of variant peptide epitopes.
- [0080] "Human Leukocyte Antigen" or "HLA" is a human class I or class II Major Histocompatibility Complex (MHC) protein (see, e.g., Stites, et al., IMMUNOLOGY, 8TH ED., Lange Publishing, Los Altos, CA (1994).
- [0081] An "HLA supertype or HLA family", as used herein, describes sets of HLA molecules grouped on the basis of shared peptide-binding specificities. HLA class I molecules that share somewhat similar binding affinity for peptides bearing certain amino acid motifs are grouped into such HLA supertypes. The terms HLA superfamily, HLA supertype family, HLA family, and HLA xx-like molecules (where "xx" denotes a particular HLA type), are synonyms. See Tables 1-4.
- [0082] As used herein, "high affinity" with respect to HLA class I molecules is defined as binding with an IC₅₀, or K_D value, of 50 nM or less; "intermediate affinity" is binding with an IC₅₀ or K_D value of between about 50 and about 500 nM; "weak affinity" is binding with an IC₅₀ or K_D value between about 500 and about 5000 nM. "High affinity" with respect to binding to HLA class II molecules is defined as binding with an IC₅₀ or K_D value of 100 nM or less; "intermediate affinity" is binding with an IC₅₀ or K_D value of between about 100 and about 1000 nM. See "binding data."
- [0083] An "IC₅₀" is the concentration of peptide in a binding assay at which 50% inhibition of binding of a reference peptide is observed. Given the conditions in which the assays are run (i.e., limiting HLA proteins and labeled peptide concentrations), these values approximate K_D values. See "binding data."
- [0084] The terms "identical" or percent "identity," in the context of two or more peptide sequences or antigen fragments, refer to two or more sequences or subsequences that are the same

or have a specified percentage of amino acid residues that are the same, when compared and aligned for maximum correspondence over a comparison window, as measured using a sequence comparison algorithm or by manual alignment and visual inspection.

[0085]

An "immunogenic" peptide or an "immunogenic" epitope or "peptide epitope" is a peptide that comprises an allele-specific motif or supermotif such that the peptide will bind an HLA molecule and induce a CTL and/or HTL response. Thus, immunogenic peptides of the invention are capable of binding to an appropriate HLA molecule and thereafter inducing a cytotoxic T lymphocyte (CTL) response, or a helper T lymphocyte (HTL) response, to the peptide.

[0086]

An "infectious agent" refers to a disease-causing microorganism, including viruses, bacteria, fungi, and protozoa against which a cellular immune response, preferably a CTL response, plays a role in acquired immunity. Examples of infectious agents include viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomma virus (HPV), Influenza virus, Dengue virus, Epstein-Barr virus, bacteria such as Mycobacterium tuberculosis and Chlamydia, fungi such as Candida albicans, Cryptococcus neoformans, Coccidoides spp., Histoplasma spp., and Aspergillus fumigatis, protozoa such as Plasmodium spp., including P. falciparum, Trypanosoma spp., Schistosoma spp., Leishmania spp and the like. Preferred infectious agents include HIV, HBV, HCV, HPV, Epstein-Barr virus, Plasmodium falciparum, Influenza virus and Dengue virus.

[0087]

The phrases "isolated" or "biologically pure" refer to material which is substantially or cssentially free from components which normally accompany the material as it is found in its native state. Thus, isolated peptides in accordance with the invention preferably do not contain materials normally associated with the peptides in their in situ environment. An "isolated" epitope refers to an epitope that does not include the whole sequence of the antigen or polypeptide from which the epitope was derived. Typically the "isolated" epitope does not have attached thereto additional amino acids that result in a sequence that has 100% identity with a native sequence. The native sequence can be a sequence such as a tumor-associated antigen from which the epitope is derived. Thus, the term "isolated" means that the material is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or peptide present in a living animal is not isolated, but the same polynucleotide or peptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such a polynucleotide could be part of a vector, and/or such a polynucleotide or peptide could be part of a composition, and still be "isolated" in that such vector or composition is not part of its natural environment. Isolated RNA molecules include in vivo or in vitro RNA

transcripts of the DNA molecules of the present invention, and further include such molecules produced synthetically.

- [0088] "Major Histocompatibility Complex" or "MHC" is a cluster of genes that plays a role in control of the cellular interactions responsible for physiologic immune responses. In humans, the MHC complex is also known as the human leukocyte antigen (HLA) complex. For a detailed description of the MHC and HLA complexes, see, Paul, FUNDAMENTAL IMMUNOLOGY, 3RD ED., Raven Press, New York (1993).
- [0089] The term "motif" refers to a pattern of residues in an amino acid sequence of defined length, preferably a peptide of less than about 15 amino acids in length, or less than about 13 amino acids in length, usually from about 8 to about 13 amino acids (e.g., 8, 9, 10, 11, 12, or 13) for a class I HLA motif and from about 6 to about 25 amino acids (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) for a class II HLA motif, which is recognized by a particular HLA molecule. Motifs are typically different for each HLA protein encoded by a given human HLA allele. These motifs often differ in their pattern of the primary and secondary anchor residues. See Tables 1-3.
- [0090] A "native" or a "wild type" sequence refers to a sequence found in nature.
- [0091] A "negative binding residue" or "deleterious residue" is an amino acid which, if present at certain positions (typically not primary anchor positions) in a peptide epitope, results in decreased binding affinity of the peptide for the peptide's corresponding HLA molecule.
- [0092] The term "peptide" is used interchangeably with "oligopeptide" in the present specification to designate a series of residues, typically L-amino acids, connected one to the other, typically by peptide bonds between the α-amino and carboxyl groups of adjacent amino acids.
- A "PanDR binding" peptide or "PADRE®" peptide (Epimmune, San Diego, CA) is a member of a family of molecules that binds more than one HLA class II DR molecule. The pattern that defines the PADRE® family of molecules can be referred to as an HLA Class II supermotif. A PADRE® molecule binds to HLA-DR molecules and stimulates in vitro and in vivo human helper T lymphocyte (HTL) responses. For a further definition of the PADRE® family, see copending application US serial Nos. 09/709,774, filed November 11, 2000; and 09/707,738, filed November 6, 2000; PCT publication Nos WO 95/07707, and WO 97/26784; U.S. Patent Nos. 5,736,142 issued April 7, 1998; 5,679,640, issued October 21, 1997; and 6,413,935, issued July 2, 2002.
- [0094] "Pharmaceutically acceptable" refers to a generally non-toxic, inert, and/or physiologically compatible composition or component of a composition.

[0095] A "pharmaceutical excipient" or "excipient" comprises a material such as an adjuvant, a carrier, pH-adjusting and buffering agents, tonicity adjusting agents, wetting agents, preservatives, and the like. A "pharmaceutical excipient" is an excipient which is pharmaceutically acceptable.

[0096]A "primary anchor residue" is an amino acid at a specific position along a peptide sequence which is understood to provide a contact point between the immunogenic peptide and the HLA molecule. One, two or three, primary anchor residues within a peptide of defined length generally defines a "motif" for an immunogenic peptide. These residues are understood to fit in close contact with peptide binding grooves of an HLA molecule, with their side chains buried in specific pockets of the binding grooves themselves. In one embodiment of an HLA class I motif, the primary anchor residues are located at position 2 (from the amino terminal position) and at the carboxyl terminal position of a peptide epitope in accordance with the invention. The primary anchor positions for each motif and supermotif of HLA Class I are set forth in Tables 1-2. For example, analog peptides can be created by altering the presence or absence of particular residues in these anchor positions. Such analogs are used to modulate the binding affinity of an epitope comprising a particular motif or supermotif. A "preferred primary anchor residue" is an anchor residue of a motif or supermotif that is associated with optimal binding. Preferred primary anchor residues are indicated in bold-face in Tables 1-2. A "tolerated primary anchor residue" is an anchor residue of a motif or supermotif that is associated with binding to a lesser extent than a preferred residue. Tolerated primary anchor residues are indicated in italicized text in Tables 1-2.

[0097] "Promiscuous recognition" by a TCR is where a distinct peptide is recognized by the various T cell clones in the context of various HLA molecules. Promiscuous binding by an HLA molecule is synonymous with cross-reactive binding.

[0098] A "protective immune response" or "therapeutic immune response" refers to a CTL and/or an HTL response to an antigen derived from an antigen of an infectious agent, which in some way prevents or at least partially arrests disease symptoms, side effects or progression. The immune response may also include an antibody response which has been facilitated by the stimulation of helper T cells.

[0099] By "ranking" the variants in a population of peptide epitopes is meant ordering each variant by its frequency of occurrance relative to the other variants.

[00100] The term "residue" refers to an amino acid or amino acid mimetic incorporated into a peptide or protein by an amide bond or amide bond mimetic.

[00101] A "secondary anchor residue" is an amino acid at a position other than a primary anchor position in a peptide which may influence peptide binding. A secondary anchor residue occurs at a significantly higher frequency amongst HLA-bound peptides than would be expected by random

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distribution of amino acids at a given position. A secondary anchor residue can be identified as a residue which is present at a higher frequency among high or intermediate affinity binding peptides, or a residue otherwise associated with high or intermediate affinity binding. The secondary anchor residues are said to occur at "secondary anchor positions." For example, analog peptides can be created by altering the presence or absence of particular residues in these secondary anchor positions. Such analogs are used to finely modulate the binding affinity of an epitope comprising a particular motif or supermotif. The terminology "fixed peptide" is generally used to refer to an analog peptide that has changes in primary anchore position; not secondary.

- [00102] A "subdominant epitope" is an epitope which evokes little or no response upon immunization with a whole antigen or a fragment of the whole antigen comprising a subdominant epitope and a dominant epitope, which comprise the epitope, but for which a response can be obtained by immunization with an isolated peptide, and this response (unlike the case of cryptic epitopes) is detected when whole antigen or a fragment of the whole antigen comprising a subdominant epitope and a dominant epitope is used to recall the response in vitro or in vivo.
- [00103] A "supermotif" is a peptide binding specificity shared by HLA molecules encoded by two or more HLA alleles. Preferably, a supermotif-bearing peptide is recognized with high or intermediate affinity (as defined herein) by two or more HLA antigens.
- [00104] "Synthetic peptide" refers to a peptide that is abtained from a non-natural source, e.g., is man-made. Such peptides may be produced using such methods as chemical synthesis or recombinant DNA technology. "Synthetic peptides" include "fusion proteins."
- [00105] As used herein, a "vaccine" is a composition used for vaccination, e.g., for prophylaxis or therapy, that comprises one or more peptides of the invention. There are numerous embodiments of vaccines in accordance with the invention, such as by a cocktail of one or more peptides; one or more peptides of the invention comprised by a polyepitopic peptide; or nucleic acids that encode such peptides or polypeptides, e.g., a minigene that encodes a polyepitopic peptide. The "one or more peptides" can include any whole unit integer from 1-150, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 or more peptides of the invention. The peptides or polypeptides can optionally be modified, such as by lipidation, addition of targeting or other sequences. HLA class I-binding peptides of the invention can be linked to HLA class II-binding peptides, e.g., a PADRE® universal HTL-bindind peptide, to facilitate activation of both cytotoxic T lymphocytes and helper T lymphocytes. Vaccines can comprise peptide pulsed antigen presenting cells, e.g., dendritic cells.
- [00106] A "variant of a peptide epitope" refers to a peptide that is identified from a different viral strain at the same position in an aligned sequence, and that varies by one or

more amino acids from the parent peptide epitope. Examples of peptide epitope variants include those shown in Tables 6-9 and Figures 1A-4. A "variant of an antigen" refers to an antigen that comprises at least one variant of a peptide epitope. Examples of antigen variants include those listed by sequence and/or accession number in Tables 10-22. A "variant of an infectious agent" refers to an infectious agent whose genome encodes at least one variant of an antigen. Variants of infectious agents are related viral, bacterial, funagl, or protozoan strains or isolates that vary in sequence but cause the same disease symptoms. Examples of infectious agent variants include HIV Clade A, B, and C subtypes, HBV subtypes adr, ayr, adw, and ayw, HCV types 1, 2, 3, 4, 5, and 6, HPV strains 1-92 (preferably strains 16, 18, 31, 33, 45, 52, 56, and 58) (see Table 10, listing accession numbers for the complete genome sequences of 167 HIV variants; Table 22, showing an alignment of the complete polyprotein sequences of 50 HCV variants) (see also, Human Retroviruses and AIDS 2000: A Compilation and Analysis of Nucleic Acid and Amino Acid Sequences, Kuiken CL, et al., Eds. Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, NM).

[00107] The nomenclature used to describe peptides/proteins follows the conventional practice wherein the amino group is presented to the left (the N-terminus) and the carboxyl group to the right (the C-terminus) of each amino acid residue. When amino acid residue positions are referred to in a peptide epitope they are numbered in an amino to carboxyl direction with position one being the position closest to the amino terminal end of the epitope, or the peptide or protein of which it may be a part. In the formulae representing selected specific embodiments of the present invention, the amino- and carboxyl-terminal groups, although not specifically shown, are in the form they would assume at physiologic pH values, unless otherwise specified. In the amino acid structure formulae, each residue is generally represented by standard three letter or single letter designations. The L-form of an amino acid residue is represented by a capital single letter or a capital first letter of a three-letter symbol, and the D-form for those amino acids having D-forms is represented by a lower case single letter or a lower case three letter symbol. However, when three letter symbols or full names are used without capitals, they may refer to L amino acids. Glycine has no asymmetric carbon atom and is simply referred to as "Gly" or "G". The amino acid sequences of peptides set forth herein are generally designated using the standard single letter symbol. (A, Alanine; C, Cysteine; D, Aspartic Acid; E, Glutamic Acid; F, Phenylalanine; G, Glycine; H, Histidine; I, Isoleucine; K, Lysine; L, Leucine; M, Methionine; N, Asparagine; P, Proline; Q, Glutamine; R, Arginine; S, Serine; T, Threonine; V, Valine; W, Tryptophan; and Y, Tyrosine.) In addition to these symbols, "B"in the single letter abbreviations used herein

designates α -amino butyric acid. In some embodiments, α -amino butyric acid may be replaced with cysteine.

Acronyms used herein are as follows:

APC: Antigen presenting cell CD3: Pan T cell marker

CD4: Helper T lymphocyte marker CD8: Cytotoxic T lymphocyte marker

CEA: Carcinoembryonic antigen (see, e.g., SEQ ID NO: 363)

CTL: Cytotoxic T lymphocyte

DC: Dendritic cells. DC functioned as potent antigen presenting cells by stimulating

cytokine release from CTL lines that were specific for a model peptide derived from hepatitis B virus. *In vivo* experiments using DC pulsed *ex vivo* with an HBV peptide epitope have stimulated CTL immune responses *in vivo* following delivery

to naïve mice.

DLT: Dose-limiting toxicity, an adverse event related to therapy.

DMSO: Dimethylsulfoxide

ELISA: Enzyme-linked immunosorbant assay

E:T: Effector:Target ratio

G-CSF: Granulocyte colony-stimulating factor

GM-CSF: Granulocyte-macrophage (monocyte)-colony stimulating factor

HBV: Hepatitis B virus

HER2/neu: A tumor associated antigen; c-erbB-2 is a synonym (see, e.g., SEQ ID NO: 364)

HLA: Human leukocyte antigen

IILA-DR: Human lcukocyte antigen class II

HPLC: High Performance Liquid Chromatography

HTC: Helper T Cell

HTL: Helper T Lymphocyte. A synonym for HTC.

ID: Identity

IFNγ: Interferon gamma IL-4: Interleukin-4 IV: Intravenous

LU_{30%}: Cytotoxic activity for 10⁶ effector cells required to achieve 30% lysis of a target

cell population, at a 100:1 (E:T) ratio.

MAb: Monoclonal antibody

MAGE: Melanoma antigen (see, e.g., SEQ ID NO: 365 and 366 for MAGE2 and MAGE3)

MLR: Mixed lymphocyte reaction

MNC: Mononuclear cells PB: Peripheral blood

PBMC: Peripheral blood mononuclear cell

ProGPTM: ProgenipoietinTM product (Searle, St. Louis, MO), a chimeric flt3/G-

CSF receptor agonist.

SC: Subcutaneous

S.E.M.: Standard error of the mean

QD: Once a day dosing

TAA: Tumor Associated Antigen
TNF: Tumor necrosis factor
WBC: White blood cells

[00108] The following describes the peptides, nucleic acid molecules, compositions, and methods of the invention in more detail.

Methods of Identifying Candidate Peptide Epitopes

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[00109] The present invention is directed to methods for selecting a variant of a peptide epitope which induces a CTL response against another variant(s) of the peptide epitope, by determining whether the variant comprises only conserved residues, as defined herein, at non-anchor positions in comparison to the other variant(s).

In some embodiments, antigen sequences from a population of an infectious agent, said antigens comprising variants of a peptide epitope, are optionally aligned (manually or by computer) along their length, preferably their full length. Variant(s) of a peptide epitope (preferably naturally occurring variants), each 8-11 amino acids in length and comprising the same MHC class I supermotif or motif, are identified manually or with the aid of a computer. In some embodiments, a variant is optionally chosen which comprises preferred anchor residues of said motif and/or which occurs with high frequency within the population of variants. In other embodiments, a variant is randomly chosen. The randomly or otherwise chosen variant is compared to from one to all the remaining variant(s) to determine whether it comprises only conserved residues in the non-anchor positions relative to from one to all the remaining variant(s).

[00111] The present invention is also directed to variants identified by the methods above; peptides comprising such variants; nucleic acids encoding such variants and peptides; cells comprising such variants, and/or peptides, and/or nucleic acids; compositions comprising such variants, and/or peptides, and/or nucleic acids, and/or cells; as well as therapeutic and diagnostic methods for using such variants, peptides, nucleic acids, cells, and compositions.

[00112] In some embodiments, the invention is directed to a method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising

a) identifying, from a particular antigen of an infectious agent, variants of a peptide epitope 8-11 amino acids in length, each variant comprising primary anchor residues of the same HLA class I binding motif; and

- b) determining whether one of said variants comprises only conserved non-anchor residues in comparison to at least one remaining variant, thereby identifying a candidate peptide epitope.
- [00113] In some embodiments, (b) comprises identifying a variant which comprises only conserved non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- [00114] In some embodiments, the invention is directed to a method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, variants of a peptide epitope 8-11 amino acids in length, each variant comprising primary anchor residues of the same HLA class I binding motif;
 - determining whether each of said variants comprises conserved, semiconserved or non-conserved non-anchor residues in comparison to each of the remaining variants; and
 - c) identifying a variant which comprises only conserved non-anchor residues in comparison to at least one remaining variant.
- [00115] In some embodiments, (c) comprises identifying a variant which comprises only conservative non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- [00116] In some embodiments, the invention is directed to a method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, a
 population of variants of a peptide epitope 8-11 amino acids in length,
 each peptide epitope comprising primary anchor residues of the same
 HLA class I binding motif;
 - b) choosing a variant selected from the group consisting of:
 - a variant which comprises preferred primary anchor residues of said motif; and

- ii) a variant which occurs with high frequency within the population of variants; and
- c) determining whether the variant of (b) comprises only conserved nonanchor residues in comparison to at least one remaining variant, thereby identifying a candidate peptide epitope.
- [00117] In some embodiments, (c) comprises identifying a variant which comprises only conservative non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- [00118] In some embodiments, the invention is directed to method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, a
 population of variants of a peptide epitope 8-11 amino acids in length,
 each peptide epitope comprising primary anchor residues of the same
 HLA class I binding motif;
 - b) choosing a variant selected from the group consisting of:
 - a variant which comprises preferred primary anchor residues of said motif; and
 - a variant which occurs with high frequency within the population of variants; and
 - c) determining whether the variant of (b) comprises conserved, semiconserved or non-conserved non-anchor residues in comparison to each of the remaining variants; and
 - d) identifying a variant which comprises only conserved non-anchor residues in comparison to at least one remaining variant.
- [00119] In some embodiments, (d) comprises identifying a variant which comprises only conservative non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- [00120] In some embodiments, (a) comprises aligning the sequences of said antigens.

- [00121] In some embodiments, (b) comprises comprises choosing a variant which comprises preferred primary anchor residues of said motif.
- [00122] In some embodiments, (b) comprises comprises choosing a variant which occurs with high frequency within said population.
- [00123] In some embodiments, (b) comprises ranking said variants by frequency of occurrence within said population.
- [00124] In some embodiments, (b) comprises choosing a variant which comprises preferred primary anchor residues of said motif and which occurs with high frequency within said population.
- [00125] In some embodiments, (b) comprises ranking said variants by frequency of occurrence within said population.
- [00126] In some embodiments, the identified variant comprises the fewest conserved anchor residues in comparison to each of the remaining variants.
- [00127] In some embodiments, the remaining variants comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, or 300 variants.
- [00128] In some embodiments, the infectious agent is selected from the group consisting of: HIV, HBV, HCV, HPV, Plasmodium falciparum, Influenza virus, and Dengue virus, Epstein-Barr virus, Mycobacterium tuberculosis, Chlamydia, Candida albicans, Cryptococcus neoformans, Coccidoides spp., Histoplasma spp., Aspergillus fumigatis, Plasmodium spp., Trypanosoma spp., Schistosoma spp., and Leishmania spp.
- [00129] In some embodiments, the infectious agent is selected from the group consisting of: HIV, HBV, HCV, HPV, Plasmodium falciparum, Influenza virus, and Dengue virus.
- [00130] In some embodiments, the infectious agent is HIV and the antigen is selected from the group consisting of: Gag, Env, Pol, Nef, Rev, Tat, Vif, Vpr, and Vpu.
- [00131] In some embodiments, the infectious agent is HBV and the antigen is selected from the group consisting of: Pol, Env, Core, and NS1/Env2.
- [00132] In some embodiments, the infectious agent is HCV and the antigen is selected from the group consisting of: Core, E1, E2, NS1, NS2, NS3, NS4, and NS5.
- [00133] In some embodiments, the infectious agent is HPV and the antigen is selected from the group consisting of: E1, E2, E3, E4, E5, E6, E7, L1, and L2.

- [00134] In some embodiments, the infectious agent is *Plasmodium falciparum* and the antigen is selected from the group consisting of: CSP, SSP2, EXP1, LSA1.
- [00135] In some embodiments, the selected variant and the at least one remaining variant comprise different primary anchor residues of the same motif or supermotif.
- [00136] In some embodiments, the motif or supermotif is selected from the group consisting of those in Tables 1-2.
- [00137] In some embodiments, the conserved non-anchor residues are at any of positions 3-7 of said variant.
- [00138] In some embodiments, the variant comprises only 1-3 conserved non-anchor residues compared to at least one remaining variant.
- [00139] In some embodiments, the variant comprises only 1-2 conserved non-anchor residues compared to at least one remaining variant.
- [00140] In some embodiments, the variant comprises only 1 conserved non-anchor residue compared to at least one remaining variant.
- [00141] In some embodiments, the infectious agent is HPV, and further wherein, the HPV infectious agent is selected from the group consisting of HPV strains 16, 18, 31, 33, 45, 52, 56, and 58.
- [00142] In some embodiments, the variants are a population of naturally occurring variants.
- [00143] Optional Alignment. Optionally, antigen sequences, either full-length or partial, may be aligned mannually or by computer. Convenient computer programs for aligning multiple sequences include Omiga, Oxford software, version 1.1.3, using ClustalW alignment, using an open gap penalty of 10.0, extend gap penalty of 0.05, and delay divergent sequences of 40.0 (See, e.g., Table 21); and BLASTP 2.2.5 (Nov-16-2002) (Altschul, S.F., et al., Nucleic Acids Res. 25:3389-3402 (1997)) using a cutoff = 3e-88 (to select human sequences) (see, e.g., Table 20). Alternatively, alignments may be obtained through publicly available sources such as published journal articles and published patent documents or as disclosed herein (see, e.g., Tables 10-22).
- [00144] HLA Class I Motifs Indicative of CTL Inducing Peptide Epitopes. A large fraction of HLA class I and class II molecules can be classified into a relatively few supertypes, each respective supertype characterized by largely overlapping peptide binding repertoires, and consensus structures of the main peptide binding pockets. Thus,

peptides of the present invention are preferably identified by the primary residues of any one of several HLA-specific amino acid motifs, or if the presence of the motif corresponds to the ability to bind several allele-specific HLA antigens, a supermotif (see, e.g., Tables 1-2). The preferred primary residues are indicated in bold, while the tolerated primary residues are indicated by italics.

- [00145] The primary anchor residues of the HLA class I peptide epitope supermotifs and motifs are summarized in Tables 1-2. Preferred primary anchors are shown in bold, while tolerated primary anchors are shown in italics. Primary and secondary anchor positions for HLA Class I are summarized in Table 3. Allele-specific HLA molecules that fall within the various HLA class I supertypes are listed in Table 4. In some cases, patterns of amino acid residues are present in both a motif and a supermotif. The relationship of a particular motif and any related supermotif is indicated in the description of the individual motifs.
- [00146] Thus, the peptide motifs and supermotifs described below, and summarized in Tables 1-2, provide guidance for the identification and use of peptide epitopes comprising primary anchor residues of motifs or supermotifs in accordance with the invention.
- [00147] Allele-specific HLA molecules that comprise HLA class I supertype families are listed in Table 4.
- [00148] HLA-A1 supermotif. The HLA-A1 supermotif is characterized by the presence in peptide ligands of a small (T or S) or hydrophobic (L, I, V, or M) primary anchor residue in position 2, and an aromatic (Y, F, or W) primary anchor residue at the C-terminal position of the epitope. The corresponding family of HLA molecules that bind to the A1 supermotif (i.e., the HLA-A1 supertype) is comprised of at least A*0101, A*2601, A*2602, A*2501, and A*3201 (see, e.g., DiBrino, M. et al., J. Immunol. 151:5930, 1993; DiBrino, M. et al., J. Immunol. 152:620, 1994; Kondo, A. et al., Immunogenetics 45:249, 1997). Other allele-specific HLA molecules predicted to be members of the A1 superfamily are shown in Table 4. Peptides binding to each of the individual HLA proteins can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.
- [00149] HLA-A2 supermotif. Primary anchor specificities for allele-specific HLA-A2.1 molecules (see, e.g., Falk et al., Nature 351:290-296, 1991; Hunt et al., Science 255:1261-1263, 1992; Parker et al., J. Immunol. 149:3580-3587, 1992; Ruppert et al., Cell 74:929-937, 1993) and cross-reactive binding among HLA-A2 and -A28 molecules have been

described. (See, e.g., Fruci et al., Human Immunol. 38:187-192, 1993; Tanigaki et al., Human Immunol. 39:155-162, 1994; Del Guercio et al., J. Immunol. 154:685-693, 1995; Kast et al., J. Immunol. 152:3904-3912, 1994 for reviews of relevant data.) These primary anchor residues define the HLA-A2 supermotif; which presence in peptide ligands corresponds to the ability to bind several different HLA-A2 and -A28 molecules. The HLA-A2 supermotif comprises peptide ligands with L, I, V, M, A, T, or Q as a primary anchor residue at position 2 and L, I, V, M, A, or T as a primary anchor residue at the C-terminal position of the epitope.

- [00150] The corresponding family of HLA molecules (i.e., the HLA-A2 supertype that binds these peptides) is comprised of at least: A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, A*0207, A*0209, A*0214, A*6802, and A*6901. Other allele-specific HLA molecules predicted to be members of the A2 superfamily are shown in Table 4. As explained in detail below, binding to each of the individual allele-specific HLA molecules can be modulated by substitutions at the primary anchor and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.
- [00151] The motifs comprising the primary anchor residues V, A, T, or Q at position 2 and L, I, V, A, or T at the C-terminal position are those most particularly relevant to the invention claimed herein.
- peptide ligands of A, L, I, V, M, S, or, T as a primary anchor at position 2, and a positively charged residue, R or K, at the C-terminal position of the epitope, e.g., in position 9 of 9-mers (see, e.g., Sidney et al., Hum. Immunol. 45:79, 1996). Exemplary members of the corresponding family of HLA molecules (the HLA-A3 supertype) that bind the A3 supermotif include at least A*0301, A*1101, A*3101, A*3301, and A*6801. Other allele-specific HLA molecules predicted to be members of the A3 supertype are shown in Table 4. As explained in detail below, peptide binding to each of the individual allele-specific HLA proteins can be modulated by substitutions of amino acids at the primary and/or secondary anchor positions of the peptide, preferably choosing respective residues specified for the supermotif.
- [00153] HLA-A24 supermotif. The HLA-A24 supermotif is characterized by the presence in peptide ligands of an aromatic (F, W, or Y) or hydrophobic aliphatic (L, I, V, M, or T) residue as a primary anchor in position 2, and Y, F, W, L, I, or M as primary anchor at the C-terminal position of the epitope (see, e.g., Sette and Sidney, Immunogenetics, in press,

1999). The corresponding family of HLA molecules that bind to the A24 supermotif (i.e., the A24 supertype) includes at least A*2402, A*3001, and A*2301. Other allele-specific HLA molecules predicted to be members of the A24 supertype are shown in Table 4. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

[00154] HLA-B7 supermotif. The HLA-B7 supermotif is characterized by peptides bearing proline in position 2 as a primary anchor, and a hydrophobic or aliphatic amino acid (L, I, V, M, A, F, W, or Y) as the primary anchor at the C-terminal position of the epitope. The corresponding family of HLA molecules that bind the B7 supermotif (i.e., the HLA-B7 supertype) is comprised of at least twenty six HLA-B proteins including: B*0702, B*0703, B*0704, B*0705, B*1508, B*3501, B*3502, B*3503, B*3504, B*3505, B*3506, B*3507, B*3508, B*5101, B*5102, B*5103, B*5104, B*5105, B*5301, B*5401, B*5501, B*5502, B*5601, B*5602, B*6701, and B*7801 (see, e.g., Sidney, et al., J. Immunol. 154:247, 1995; Barber, et al., Curr. Biol. 5:179, 1995; Hill, et al., Nature 360:434, 1992; Rammensee, et al., Immunogenetics 41:178, 1995 for reviews of relevant data). Other allele-specific HLA molecules predicted to be members of the B7 supertype are shown in Table 4. As explained in detail below, peptide binding to each of the individual allele-specific HLA proteins can be modulated by substitutions at the primary and/or secondary anchor positions of the peptide, preferably choosing respective residues specified for the supermotif.

in peptide ligands of a positively charged (R, H, or K) residue as a primary anchor at position 2, and a hydrophobic (F, Y, L, W, M, I, A, or V) residue as a primary anchor at the C-terminal position of the epitope (see, e.g., Sidney and Sette, Immunogenetics, in press, 1999). Exemplary members of the corresponding family of HLA molecules that bind to the B27 supermotif (i.e., the B27 supertype) include at least B*1401, B*1402, B*1509, B*2702, B*2703, B*2704, B*2705, B*2706, B*3801, B*3901, B*3902, and B*7301. Other allele-specific HLA molecules predicted to be members of the B27 supertype are shown in Table 4. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

- in peptide ligands of negatively charged (D or E) residues as a primary anchor in position 2, and hydrophobic residues (F, W, Y, L, I, M, V, or A) as a primary anchor at the C-terminal position of the epitope (see, e.g., Sidney et al., Immunol. Today 17:261, 1996). Exemplary members of the corresponding family of HLA molecules that bind to the B44 supermotif (i.e., the B44 supertype) include at least: B*1801, B*1802, B*3701, B*4001, B*4002, B*4006, B*4402, B*4403, and B*4006. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions; preferably choosing respective residues specified for the supermotif.
- in peptide ligands of a small aliphatic residue (A, S, or T) as a primary anchor residue at position 2, and an aromatic or hydrophobic residue (F, W, Y, L, I, V, M, or A) as a primary anchor residue at the C-terminal position of the epitope (see, e.g., Sidney and Sette, Immunogenetics, in press, 1999 for reviews of relevant data). Exemplary members of the corresponding family of HLA molecules that bind to the B58 supermotif (i.e., the B58 supertype) include at least: B*1516, B*1517, B*5701, B*5702, and B*5801. Other allele-specific HLA molecules predicted to be members of the B58 supertype are shown in Table 4. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.
- in peptide ligands of the polar aliphatic residue Q or a hydrophobic aliphatic residue (L, V, M, I, or P) as a primary anchor in position 2, and a hydrophobic residue (F, W, Y, M, I, V, L, or A) as a primary anchor at the C-terminal position of the epitope (see, e.g., Sidney and Sette, Immunogenetics, in press, 1999). Exemplary members of the corresponding family of HLA molecules that bind to the B62 supermotif (i.e., the B62 supertype) include at least: B*1501, B*1502, B*1513, and B5201. Other allele-specific HLA molecules predicted to be members of the B62 supertype are shown in Table 4. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.
- [00159] HLA-A1 motif. The HLA-A1 motif is characterized by the presence in peptide ligands of T, S, or M as a primary anchor residue at position 2 and the presence of Y as a

primary anchor residue at the C-terminal position of the epitope. An alternative allelespecific A1 motif is characterized by a primary anchor residue at position 3 rather than position 2. This motif is characterized by the presence of D, E, A, or S as a primary anchor residue in position 3, and a Y as a primary anchor residue at the C-terminal position of the epitope (see, e.g., DiBrino et al., J. Immunol., 152:620, 1994; Kondo et al., Immunogenetics 45:249, 1997; and Kubo et al., J. Immunol. 152:3913, 1994 for reviews of relevant data). Peptide binding to HLA A1 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

[00160] Those epitopes comprising T, S, or M at position 2 and Y at the C-terminal position are also HLA-A1 supermotif-bearing peptide epitopes, as these residues are a subset of the A1 supermotif primary anchors.

HLA-A*0201 motif. An HLA-A2*0201 motif was determined to be characterized [00161] by the presence in peptide ligands of L or M as a primary anchor residue in position 2, and L or V as a primary anchor residue at the C-terminal position of a 9-residue peptide (see, e.g., Falk et al., Nature 351:290-296, 1991) and was further found to comprise an I at position 2 and I or A at the C-terminal position of a nine amino acid peptide (see, e.g., Hunt et al., Science 255:1261-1263, March 6, 1992; Parker et al., J. Immunol. 149:3580-3587, 1992). The A*0201 allele-specific motif has also been defined by the present inventors to additionally comprise V, A, T, or Q as a primary anchor residue at position 2, and M or T as a primary anchor residue at the C-terminal position of the epitope (see, e.g., Kast et al., J. Immunol. 152:3904-3912, 1994). Thus, the HLA-A*0201 motif comprises peptide ligands with L, I, V, M, A, T, or Q as primary anchor residues at position 2 and L, I, V, M, A, or T as a primary anchor residue at the C-terminal position of the epitope. The preferred and tolerated residues that characterize the primary anchor positions of the HLA-A*0201 motif are identical to the residues describing the A2 supermotif. (For reviews of relevant data, see, e.g., Del Guercio et al., J. Immunol. 154:685-693, 1995; Ruppert et al., Cell 74:929-937, 1993; Sidney et al., Immunol. Today 17:261-266, 1996; Sette and Sidney, Curr. Opin. in Immunol. 10:478-482, 1998). Secondary anchor residues that characterize the A*0201 motif have additionally been defined (see, e.g., Ruppert et al., Cell 74:929-937, 1993). These are shown in Table 3. Peptide binding to HLA-A*0201 molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

- [00162] HLA-A3 motif. The HLA-A3 motif is characterized by the presence in peptide ligands of L, M, V, I, S, A, T, F, C, G, or D as a primary anchor residue at position 2, and the presence of K, Y, R, H, F, or A as a primary anchor residue at the C-terminal position of the epitope (see, e.g., DiBrino et al., Proc. Natl. Acad. Sci USA 90:1508, 1993; and Kubo et al., J. Immunol. 152:3913-3924, 1994). Peptide binding to HLA-A3 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.
- [00163] The A3 supermotif primary anchor residues comprise a subset of the A3- and A11- allele specific motif primary anchor residues.
- [00164] HLA-A11 motif. The HLA-A11 motif is characterized by the presence in peptide ligands of V, T, M, L, I, S, A, G, N, C, D, or F as a primary anchor residue in position 2, and K, R, Y, or H as a primary anchor residue at the C-terminal position of the epitope (see, e.g., Zhang et al., Proc. Natl. Acad. Sci USA 90:2217-2221, 1993; and Kubo et al., J. Immunol. 152:3913-3924, 1994). Peptide binding to HLA-A11 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.
- [00165] There is extensive overlap between the A3 and A11 motif primary anchor specificities.
- [00166] HLA-A24 motif. The HLA-A24 motif is characterized by the presence in peptide ligands of Y, F, W, or M as a primary anchor residue in position 2, and F, L, I, or W as a primary anchor residue at the C-terminal position of the epitope (see, e.g., Kondo et al., J. Immunol. 155:4307-4312, 1995; and Kubo et al., J. Immunol. 152:3913-3924, 1994). Peptide binding to HLA-A24 molecules can be modulated by substitutions at primary and/or secondary anchor positions; preferably choosing respective residues specified for the motif.
- [00167] The primary anchor residues characterizing the A24 allele-specific motif comprise a subset of the A24 supermotif primary anchor residues.
- [00168] Computer or Manual Screening. Peptides bearing HLA Class I or Class II supermotifs or motifs may be identified by computer searches or manually, e.g., as follows. In utilizing computer screening to identify peptide epitopes, a protein sequence or translated sequence may be analyzed using software developed to search for motifs, for example the "FINDPATTERNS' program (Devereux, et al. Nucl. Acids Res. 12:387-395,

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1984) or MotifSearch 1.4 software program (D. Brown, San Diego, CA) to identify potential peptide sequences containing appropriate HLA binding motifs. The identified peptides can be scored using customized polynomial algorithms to predict their capacity to bind specific HLA class I or class II alleles. As appreciated by one of ordinary skill in the art, a large array of computer programming software and hardware options are available in the relevant art which can be employed to implement the motifs in order to evaluate (e.g., without limitation, to identify epitopes, identify epitope concentration per peptide length, or to generate analogs) known or unknown peptide sequences.

[00169] Translated antigen protein sequences may be analyzed using a text string search software program, e.g., MotifSearch 1.4 (D. Brown, San Diego) to identify potential peptide sequences containing appropriate HLA binding motifs; alternative programs are readily produced in accordance with information in the art in view of the motif/supermotif disclosure herein. Furthermore, such calculations can be made mentally.

[00170] Identified supermotif or motif sequences may be scored using polynomial algorithms to predict their capacity to bind to specific HLA-Class I or Class II molecules. These polynomial algorithms take into account both extended and refined motifs (that is, to account for the impact of different amino acids at different positions), and are essentially based on the premise that the overall affinity (or ΔG) of peptide-HLA molecule interactions can be approximated as a linear polynomial function of the type:

"
$$\Delta G$$
" = $a_{1i} \times a_{2i} \times a_{3i} \dots \times a_{nl}$

where a_{ji} is a coefficient which represents the effect of the presence of a given amino acid (j) at a given position (i) along the sequence of a peptide of n amino acids. The crucial assumption of this method is that the effects at each position are essentially independent of each other (i.e., independent binding of individual side-chains). When residue j occurs at position i in the peptide, it is assumed to contribute a constant amount j_i to the free energy of binding of the peptide irrespective of the sequence of the rest of the peptide. This assumption is justified by studies from our laboratories that demonstrated that peptides are bound to MHC and recognized by T cells in essentially an extended conformation (data omitted herein).

[00171] The method of derivation of specific algorithm coefficients has been described in Gulukota et al., J. Mol. Biol. 267:1258-126, 1997; (see also Sidney et al., Human Immunol. 45:79-93, 1996; and Southwood et al., J. Immunol. 160:3363-3373, 1998). Briefly, for all i positions, anchor and non-anchor alike, the geometric mean of the average

relative binding (ARB) of all peptides carrying j is calculated relative to the remainder of the group, and used as the estimate of j_i . For Class II peptides, if multiple alignments are possible, only the highest scoring alignment is utilized, following an iterative procedure. To calculate an algorithm score of a given peptide in a test set, the ARB values corresponding to the sequence of the peptide are multiplied. If this product exceeds a chosen threshold, the peptide is predicted to bind. Appropriate thresholds are chosen as a function of the degree of stringency of prediction desired.

- [00172] Additional methods to identify preferred peptide sequences, which also make use of specific motifs, include the use of neural networks and molecular modeling programs (see, e.g., Milik et al., Nature Biotechnology 16:753, 1998; Altuvia et al., Hum. Immunol. 58:1, 1997; Altuvia et al, J. Mol. Biol. 249:244, 1995; Buus, S. Curr. Opin. Immunol. 11:209-213, 1999; Brusic, V. et al., Bioinformatics 14:121-130, 1998; Parker et al., J. Immunol. 152:163, 1993; Meister et al., Vaccine 13:581, 1995; Hammer et al., J. Exp. Med. 180:2353, 1994; Sturniolo et al., Nature Biotechnol. 17:555 1999).
- [00173] Conserved, Semi-conserved, and Non-conserved Non-anchor Residues. The determination of non-anchor residues as being conserved (conservative) or semi-conserved (semi-conservative) or non-conserved (non-conservative) in comparison to the non-anchor poitions of from one to all of the remaining variant(s) is defined by as follows, the results of which are summarized in Table 5.
- [00174] Table 5 shows the similarity assignments between any given amino acid pair so that a given amino acid substitution could be characterized as being a (conservative) or semi-conserved (semi-conservative) or non-conserved (non-conservative) residue.
- [00175] The degree of similarity between amino acid pairs was quantified by averaging, for each amino acid pair, the rank coefficient scores for PAM250, hydrophobicity, and side chain volume as described below. Based on the average values of these composite rankings, Table 5 shows each pair to be conserved, semi-conserved or non-conserved.
- [00176] The Dayhoff PAM250 score (Dayhoff, M.O., et al., Atlas of Protein Sequence and Structure, Vol. 5, suppl.3. (1978) M.O. Dayhoff, ed. National Biomedical Research Foundation, Washington DC, p. 345; Creighton, T.E., Proteins: structures and molecular properties (1993) (2nd edition) W.H. Freeman and Company, NY; http://prowl.rockefeller.edu/aainfo/pam250. html) is a commonly utilized protein

alignment scoring matrix which measures the percentage of acceptable point mutations (PAM) within a defined time frame. The frequencies of these mutations are different from what would be expected from the probability of random mutations, and presumably reflect a bias due to the degree of physical and chemical similarity of the amino acid pair involved in the substitution. To obtain a score of amino acid similarity that could be standardized with other measures of similarity, the PAM250 scores were converted to a rank value, where I indicates the highest probability of being an accepted mutation.

The most commonly utilized scales to represent the relative hydrophobicity of the 20 naturally occurring amino acids (Cornette, J., et al., J. Mol. Biol. (1987) 195:659) are those developed on the basis of experimental data by Kyte and Doolittle (Kyte, J. and R.F. Doolittle, J. Mol. Biol. (1982) 157:105), and by Fauchere and Pliska (Fauchere, J. and V. Pliska, Eur. J. Med. Chem. (1983) 18:369). The Kyte/Doolittle scale measures the H₂O/organic solvent partition of individual amino acids. Because it considers the position of amino acids in folded proteins, it may most accurately reflect native hydrophobicity in the context of proteins. The Fauchere/Pliska scale measures the octanol/H₂O partitioning of N-acetyl amino acid amides, and most accurately reflects hydrophobicity in the context of denatured proteins and/or small synthetic peptides. To obtain scores for hydrophobicity, each amino acid residue was ranked on both the Kyte/Doolittle and Fauchere/Pliska hydrophobicity scales. An average rank between the two scales was calculated and the average difference in hydrophobicity for each pair was calculated.

[00178] Finally, for calculating amino acid side-chain volume, the partial volume in solution obtained by noting the increase in volume of water after adding either one molecule or one gram of amino acid residue was considered (Zamyatnin, A.A., Ann. Rev. Biophys. Bioeng. (1984) 13:145; Zamyatnin, A.A., Prog. Biophys. Mol. Biol. (1972) 24:107). The absolute difference in the partial volume of each possible pairing of the 20 naturally occurring amino acids was calculated and ranked, where 1 indicated residues with the most similar volumes, and 20 the most dissimilar.

[00179] Thus, by consulting Table 5, one can determine whether a residue in a variant is considered to be conserved, semi-conserved, or non-conserved in comparison to a residue in another variant(s). The residue of the parent variant (randomly or otherwise chosen variant) is shown across the top of Table 5, and the residue of the variant(s) it is compared with is shown below the parent residue.

[00180] As shown in Table 5, each of the amino acids shown across the top of the table bears a numerically defined relationship to the remaining 19 genetically encoded amino acids. The lower the index, the higher the conservation; the same amino acid will have a similarity assignment of 1.0; maximally different amino acids will have similarity assignments approaching 20. Using the method set forth above, amino acids which are not gene-encoded can also be assigned similarity indices and can be classified with respect to any natively occurring amino acid as conserved (conservative) or semi-conserved (semi-conservative) or non-conserved (non-conservative).

Variant Peptide Epitopes

- [00181] In some embodiments, the invention is directed to an isolated peptide comprising or consisting of a variant. In some embodiments, the invention is directed to an isolated polynucleotide encoding such a peptide.
- [00182] The isolated variants of the invention are all class I binding peptides, i.e., CTL peptides. In particular, the variants of the invention comprise a motif or supermotif, as described above. Variants of the invention are those set forth in Tables 6-9 and Figures 1A-4 (SEQ ID Nos:_). Variants of the invention may be referred to herein as "variants" and "variant peptide epitopes" or referred to by Table or referred to by SEQ ID NO. Other peptide epitopes are referred to herein as CTL epitopes or CTL peptides and HTL epitopes or HTL peptides.
- [00183] Peptides and Polynucleotides. In some embodiments, the invention is directed to an isolated peptide comprising or consisting of a variant, wherein the variant consists of a sequence selected from those in Tables 6-9 and Figures 1A-4 (SEQ ID Nos:__).
- [00184] Peptides of the invention may be fusion proteins of variant(s) to CTL epitope(s), and/or HTL epitope(s), and/or linker(s), and/or spacer(s), and/or carrier(s), and/or additional amino acid(s), and/or may comprise or consist of homopolymers of a variant or heteropolymers of more than one variant, as is described in detail below.
- [00185] Peptides which comprise a variant of the invention may comprise or consist of a fragment of an antigen ("fragment" or "antigenic fragment"), wherein the fragment comprises a variant. The fragment may be a portion of any antigen of an infectious agent, e.g., the sequences in Tables 11-22 (SEQ ID Nos:__, respectively). The variant of the invention may be within the fragment or may be linked, directly or indirectly, to the fragment.
- [00186] The fragment may comprise or consist of a region of a native antigen that contains a high concentration of class I and/or class II epitopes, preferably it contains the greatest number of epitopes per amino acid length. Such epitopes can be present in a frame-shifted manner, e.g. a 10

amino acid long peptide could contain two 9 amino acid long epitopes and one 10 amino acid long epitope.

- [00187]The fragment may be less than or equal to 600 amino acids, less than or equal to 500 amino acids, less than or equal to 400 amino acids, less than or equal to 250 amino acids, less than or equal to 100 amino acids, less than or equal to 85 amino acids, less than or equal to 75 amino acids, less than or equal to 65 amino acids, or less than or equal to 50 amino acids in length. In certain embodiments, a fragment is less than 101 amino acids in length, in any increment down to 5 amino acids in length. For example, the fragment may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length. Fragments of full length antigens may be fragments from about residue 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-680, 681-700, 701-720, 721-740, 741-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981 to the C-terminus of the antigen.
- [00188] Peptides which comprise a variant of the invention may be a fusion protein comprising one or more amino acid residues in addition to the variant or fragment. Fusion proteins include homopolymers and heteropolymers, as described below.
- [00189] In some embodiments, the peptide comprises or consists of multiple variants, e.g., 2, 3, 4, 5, 6, 7, 8, or 9 variants of the invention. In some embodiments, the peptide comprises at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 variants of the invention.
- [00190] The peptide may also be a homopolymer of one variant or the peptide may be a heteropolymer which contains at least two different variants. Polymers have the advantage of increased probability for immunological reaction and, where different variants are used to make up the polymer, the ability to induce antibodies and/or T cells that react with different antigenic determinants of the antigen(s) targeted for an immune response.
- [00191] A homopolymer may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 copies of the same variant.
- [00192] A heteropolymer may comprise one or more copies of an individual variant and one or more copies of one or more different variants of the invention. The variants that form a heteropolymer may all be from the same antigen, e.g., may be from any of those in Tables 11-22

(SEQ ID NOS:) or other antigens herein or known in the art, or may be from different antigens, preferably from infectious agents. Combinations of variants that may form a heteropolymer include, for example, Gag 545 variants EPLTSLKSLF (SEQ ID NO:) and YPLASLKSLF (SEQ ID NO:), or combinations of peptides from different tables in Tables 6-9 and/or Figures 1A-4 or those combinations in Tables 23-28. Heteropolymers may contain multiple copies of one or more variants.

- [00193] Thus, peptides of the invention such as heteropolymers may comprise a first variant and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 other (different) variants.
- [00194] In some embodiments, the peptide comprising a variant may also comprise a number of CTL and/or HTL epitopes, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 CTL and/or HTL epitopes.
- [00195] The CTL and/or HTL epitope and the variant of the invention may be from the same antigen of an infectious agent or from different antigens. Thus, for example, if the variant is from HIV pol, the CTL peptide and/or HTL peptide may also be from HIV pol. Alternatively, if the variant is from HIV pol, the CTL peptide and/or HTL peptide may be from another antigen such as HIV env or HIV vpr. As another example, if the variant is from HBV E6, the CTL peptide and/or HTL peptide may be from HBV E7. The CTL and/or IITL epitope and the variant of the invention may be from the same infectious agent or different infectious agents. Thus, for example, the variant may be from HIV, and the CTL and/or HTL epitope may be from HIV or may be from another infectious agent sush such as HBV, HCV, HPV, or Plasmodium falciparum.
- [00196] The CTL peptide and/or HTL peptide may be from other antigens including hepatitis B core and surface antigens (HBVc, HBVs), hepatitis C antigens, Epstein-Barr virus antigens, human immunodeficiency virus (HIV) antigens and human papilloma virus (HPV) antigens (in particular anitgens from HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-56 and HPV-58, Mycobacterium tuberculosis and Chlamydia. Examples of suitable fungal antigens include those derived from Candida albicans, Cryptococcus neoformans, Coccidoides spp., Histoplasma spp., and Aspergillus fumigatis. Examples of suitable protozoan parasitic antigens include those derived from Plasmodium spp., including P. falciparum, Trypanosoma spp., Schistosoma spp., Leishmania spp and the like.
- [00197] Alternatively, the CTL peptide and/or HTL peptide may be from tumor-associated antigens such as but not limited to, mclanoma antigens MAGE-1, MAGE-2, MAGE-3, MAGE-11, MAGE-A10, as well as BAGE, GAGE, RAGE, MAGE-C1, LAGE-1, CAG-3, DAM, MUC1, MUC2, MUC18, NY-ESO-1, MUM-1, CDK4, BRCA2, NY-LU-1, NY-LU-7, NY-LU-12,

CASP8, RAS, KIAA-2-5, SCCs, p53, p73, CEA, HER2/neu, Melan-A, gp100, tyrosinase, TRP2, gp75/TRP1, kallikrein, prostate-specific membrane antigen (PSM), prostatic acid phosphatase (PAP), prostate-specific antigen (PSA), PT1-1, β-catenin, PRAME, Telomcrasc, FAK, cyclin D1 protein, NOEY2, EGF-R, SART-1, CAPB, HPVE7, p15, Folate receptor CDC27, PAGE-1, and PAGE-4.

- [00198] Examples of CTL peptides and HTL peptides are disclosed in WO 01/42270, published 14 June 2001; WO 01/41788, published 14 June 2001; WO 01/42270, published 14 June 2001; WO 01/45728, published 28 June 2001; and WO 01/41787, published 14 June 2001.
- [00199] The HTL peptide may comprise a "loosely HLA-restricted" or "promiscuous" sequence. Examples of amino acid sequences that are promiscuous include sequences from antigens such as tetanus toxoid at positions 830-843 (QYIKANSKFIGITE; SEQ ID NO: 627), Plasmodium falciparum CS protein at positions 378-398 (DIEKKIAKMEKASSVFNVVNS; SEQ ID NO: 628), and Streptococcus 18kD protein at positions 116-131 (GAVDSILGGVATYGAA; SEQ ID NO: 629). Other examples include peptides bearing a DR 1-4-7 supermotif, or either of the DR3 motifs.
- [00200] The HTL peptide may comprise a synthetic peptide such as a Pan-DR-binding epitope (e.g., a PADRE® peptide, Epimmune Inc., San Diego, CA, described, for example, in U.S. Patent Number 5,736,142), for example, having the formula aKXVAAZTLKAAa, where "X" is either cyclohexylalanine, phenylalanine, or tyrosine; "Z" is either tryptophan, tyrosine, histidine or asparagine; and "a" is either D-alanine or L-alanine (SEQ ID NO: 746). Certain pan-DR binding epitopes comprise all "L" natural amino acids; these molecules can be provided as peptides or in the form of nucleic acids that encode the peptide. See also, U.S. Patent Nos. 5,679,640 and 6,413,935.
- [00201] The peptide comprising a variant may comprise additional amino acid(s). Such additional amino acids may be Ala, Arg, Asn, Asp, Cys, Gln, Gly, Glu, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Tyr, Trp, Val, amino acid mimetics, and other unnatural amino acids such as those described below. Additional amino acids may provide for ease of linking peptides one to another, for linking variants to one another, for linking variants to CTL and/or HTL epitopes, for coupling to a carrier support or larger peptide, for modifying the physical or chemical properties of the peptide or oligopeptide, or the like. Amino acids such as Ala, Arg, Asn, Asp, Cys, Gln, Gly, Glu, His, Ile, Leu, Lys, Met, Phe,

Pro, Ser, Thr, Tyr, Trp, or Val, or the like, can be introduced at the C- and/or N-terminus of the peptide and/or can be introduced internally.

- [00202] The peptide comprising a variant may comprise an amino acid spacer(s), which may be joined to the variants, CTL epitopes, HTL epitopes, carriers, etc. within a peptide or may be joined to the peptide at the N-and/or C-terminus. Thus, spacers may be at the N-terminus or C-terminus of peptide, or may be internal such that they link or join variants, CTL epitopes, HTL epitopes, carriers, additional amino acids, and/or antigenic fragments one to the other.
- The spacer is typically comprised of one or more relatively small, neutral [00203] molecules, such as amino acids or amino acid mimetics, which are substantially uncharged under physiological conditions. The spacers are typically selected from, e.g., Ala, Gly, or other neutral spacers of nonpolar amino acids or neutral polar amino acids. It will be understood that the optionally present spacer may be composed of the same residues or may be composed of one or more different residues and thus may be a homo- or heterooligomer of spacer residues. Thus, the spacer may contain more than one Ala residue (poly-alanine) or more than one Gly residue (poly-glycine), or may contain both Ala and Gly. residues, e.g., Gly. Gly-Gly-, Ser, Ser-Ser-, Gly-Ser-, Ser-Gly-, etc. When present, the spacer will usually be at least one or two residues, more usually three to six residues and sometimes 10 or more residues, e.g., 3, 4, 5, 6, 7, 8, 9, or 10, or even more residues. (Livingston, B.D. et al. Vaccine 19:4652-4660 (2000)).
- [00204] Peptides comprising a variant may comprise carrier(s) such as those well known in the art, e.g., thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly L-lysine, poly L-glutamic acid, influenza virus proteins, hepatitis B virus core protein, and the like. (See Table 29).
- [00205] In addition, the peptide comprising or consisting of a variant may be modified by terminal-NH₂ acylation, e.g., by alkanoyl (C₁-C₂₀) or thioglycolyl acetylation, terminal-carboxyl amidation, e.g., ammonia, methylamine, etc. In some instances these modifications may provide sites for linking to a support or other molecule.
- [00206] The peptides in accordance with the invention can contain modifications such as but not limited to glycosylation, side chain oxidation, biotinylation, phosphorylation, addition of a surface active material, e.g. a lipid, or can be chemically modified, e.g.,

acetylation, etc. Moreover, bonds in the peptide can be other than peptide bonds, e.g., covalent bonds, ester or ether bonds, disulfide bonds, hydrogen bonds, ionic bonds, etc.

Peptides of the present invention may contain substitutions to modify a physical property (e.g., stability or solubility) of the resulting peptide. For example, peptides may be modified by the substitution of a cysteine (C) with α -amino butyric acid ("B"). Due to its chemical nature, cysteine has the propensity to form disulfide bridges and sufficiently alter the peptide structurally so as to reduce binding capacity. Substituting α -amino butyric acid for C not only alleviates this problem, but actually improves binding and crossbinding capability in certain instances. Substitution of cysteine with α -amino butyric acid may occur at any residue of a peptide, e.g., at either anchor or non-anchor positions of a variant within a peptide, or at other positions of a peptide.

The peptides comprising a variant can comprise amino acid mimetics or unnatural [00208] amino acids, e.g. D- or L-naphylalanine; D- or L-phenylglycine; D- or L-2-thieneylalanine; D- or L-1, -2, 3, or 4-pyreneylalanine; D- or L-3 thieneylalanine; D- or L-(2-pyridinyl)alanine; D- or L-(3-pyridinyl)-alanine; D- or L-(2-pyrazinyl)-alanine; D- or L-(4-isopropyl)phenylglycine; D-(trifluoromethyl)-phenylglycine; D-(trifluoromethyl)-phenylalanine; D-ρfluorophenylalanine; Dor L-ρ-biphenylphenylalanine; or methoxybiphenylalanine; D- or L-2-indole(alkyl)alanines; and, Dor alkylalanines, where the alkyl group can be a substituted or unsubstituted methyl, ethyl, propyl, hexyl, butyl, pentyl, isopropyl, iso-butyl, sec-isotyl, iso-pentyl, or a non-acidic amino acids. Aromatic rings of a non-natural amino acid include, e.g., thiazolyl, thiophenyl, pyrazolyl, benzimidazolyl, naphthyl, furanyl, pyrrolyl, and pyridyl aromatic rings. Modified peptides that have various amino acid mimetics or unnatural amino acids are particularly useful, as they tend to manifest increased stability in vivo. Such peptides may also possess improved shelf-life or manufacturing properties.

[00209] Peptide stability can be assayed in a number of ways. For instance, peptidases and various biological media, such as human plasma and serum, have been used to test stability. See, e.g., Verhoef, et al., Eur. J. Drug Metab. Pharmacokinetics 11:291 (1986). Half-life of the peptides of the present invention is conveniently determined using a 25% human serum (v/v) assay. The protocol is generally as follows: Pooled human serum (Type AB, non-heat inactivated) is delipidated by centrifugation before use. The serum is then diluted to 25% with RPMI-1640 or another suitable tissue culture medium. At predetermined time intervals, a small amount of reaction solution is removed and added to

either 6% aqueous trichloroacetic acid (TCA) or ethanol. The cloudy reaction sample is cooled (4°C) for 15 minutes and then spun to pellet the precipitated serum proteins. The presence of the peptides is then determined by reversed-phase HPLC using stability-specific chromatography conditions.

[00210] As indicated above, the peptides in accordance with the invention can be a variety of lengths, and either in their neutral (uncharged) forms or in forms which are salts. The peptides in accordance with the invention can contain modifications such as glycosylation, side chain oxidation, or phosphorylation, generally subject to the condition that modifications do not destroy the biological activity of the peptides.

[00211] The peptides of the invention may be lyophylized, or may be in crystal form.

while still maintaining substantially all of the immunologic activity of the native protein. When possible, it may be desirable to optimize HLA class I binding epitopes of the invention to a length of about 8 to about 13 amino acid residues, for example, 8, 9, 10, 11, 12 or 13, preferably 8 to 11 or 9 to 10. It is to be appreciated that one or more epitopes in this size range can be comprised by a longer peptide (see the Definition Section for the term "epitope" for further discussion of peptide length). HLA class II binding epitopes are preferably optimized to a length of about 6 to about 30 amino acids in length, e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30, preferably to between about 13 and about 20 residues, e.g., 13, 14, 15, 16, 17, 18, 19 or 20. Preferably, the epitopes are commensurate in size with endogenously processed pathogenderived peptides or tumor cell peptides that are bound to the relevant HLA molecules. The identification and preparation of peptides of various lengths can be carried out using the techniques described herein.

[00213] Peptides in accordance with the invention can be prepared synthetically, by recombinant DNA technology or chemical synthesis, or can be isolated from natural sources such as native tumors or pathogenic organisms. Epitopes may be synthesized individually or joined directly or indirectly in a peptide. Although the peptide will preferably be substantially free of other naturally occurring host cell proteins and fragments thereof, in some embodiments the peptides may be synthetically conjugated to be joined to native fragments or particles.

[00214] The peptides of the invention can be prepared in a wide variety of ways. For relatively short sizes, the peptides can be synthesized in solution or on a solid support in

accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. (See, for example, Stewart & Young, SOLID PHASE PEPTIDE SYNTHESIS, 2D. ED., Pierce Chemical Co., 1984). Further, individual peptides can be joined using chemical ligation to produce larger peptides that are still within the bounds of the invention.

- [00215] Alternatively, recombinant DNA technology can be employed wherein a nucleotide sequence which encodes a peptide inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression. These procedures are generally known in the art, as described generally in Sambrook et al., Molecular Cloning, a Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, New York (1989). Thus, recombinant peptides, which comprise or consist of one or more epitopes of the invention, can be used to present the appropriate T cell epitope.
- [00216] Polynucleotides encoding each of the peptides above are also part of the invention. As appreciated by one of ordinary skill in the art, various nucleic acids will encode the same peptide due to the redundancy of the genetic code. Each of these nucleic acids falls within the scope of the present invention. This embodiment of the invention comprises DNA and RNA, and in certain embodiments a combination of DNA and RNA. It is to be appreciated that any polynucleotide that encodes a peptide in accordance with the invention falls within the scope of this invention.
- [00217] The polynucleotides encoding peptides contemplated herein can be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci, et al., .J. Am. Chem. Soc. 103:3185 (1981). Polynucleotides encoding peptides comprising or consisting of a variant can be made simply by substituting the appropriate and desired nucleic acid base(s) for those that encode a related (e.g., analogous) epitope.
- [00218] The polynucleotide, e.g. minigene (see below), may be produced by assembling oligonucleotides that encode the plus and minus strands of the polynucleotide, e.g. minigene. Overlapping oligonucleotides (15-100 bases long) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. A polynucleotide, e.g. minigene, encoding the peptide of the invention, can be cloned into a desired vector such as an expression vector. The coding sequence can then be provided with appropriate linkers and ligated into expression vectors commonly

available in the art, and the vectors used to transform suitable hosts to produce the desired peptide such as a fusion protein.

- [00219] A large number of such vectors and suitable host systems are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example. Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, phagescript, psiX174, pBluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia); pCR (Invitrogen). Eukaryotic: pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia); p75.6 (valentis); pCEP (Invitrogen); pCEI (Epimmune). However, any other plasmid or vector can be used as long as it is replicable and viable in the host.
- [00220] As representative examples of appropriate hosts, there can be mentioned: bacterial cells, such as *E. coli, Bacillus subtilis, Salmonella typhimurium* and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus; fungal cells, such as yeast; insect cells such as Drosophila and Sf9; animal cells such as COS-7 lines of monkey kidney fibroblasts, described by Gluzman, *Cell* 23:175 (1981), and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeI a and BHK cell lines or Bowes melanoma; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.
- [00221] Thus, the present invention is also directed to vectors, preferably expression vectors useful for the production of the peptides of the present invention, and to host cells comprising such vectors.
- [00222] Host cells are genetically engineered (transduced or transformed or transfected) with the vectors of this invention which can be, for example, a cloning vector or an expression vector. The vector can be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the polynucletides. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.
- [00223] For expression of the peptides, the coding sequence will be provided with operably linked start and stop codons, promoter and terminator regions and usually a replication system to provide an expression vector for expression in the desired cellular host. For

example, promoter sequences compatible with bacterial hosts are provided in plasmids containing convenient restriction sites for insertion of the desired coding sequence. The resulting expression vectors are transformed into suitable bacterial hosts.

- [00224] Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), α-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product.
- [00225] Yeast, insect or mammalian cell hosts may also be used, employing suitable vectors and control sequences. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell 23:175 (1981), and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. Such promoters may also be derived from viral sources, such as, e.g., human cytomegalovirus (CMV-IE promoter) or herpes simplex virus type-1 (HSV TK promoter). Nucleic acid sequences derived from the SV40 splice, and polyadenylation sites can be used to provide the required nontranscribed genetic elements.
- [00226] Polynucleotides encoding peptides of the invention may also comprise a ubiquitination signal sequence, and/or a targeting sequence such as an endoplasmic reticulum (ER) signal sequence to facilitate movement of the resulting peptide into the endoplasmic reticulum.
- [00227] Polynucleotides of the invention, e.g., minigenes, may be expressed in human cells. A human codon usage table can be used to guide the codon choice for each amino

acid. Such polynucleotides preferably comprise spacer amino acid residues between variants, such as those described above, or may comprise naturally-occurring flanking sequences adjacent to the variants (and/or CTL and HTL epitopes).

- Examples of expression vectors include attenuated viral hosts, such as vaccinia or fowlpox. As an example of this approach, vaccinia virus is used as a vector to express nucleotide sequences that encode the peptides of the invention. Vaccinia vectors and methods useful in immunization protocols are described in, e.g., U.S. Patent No. 4,722,848. Another vector is BCG (Bacille Calmette Guerin). BCG vectors are described in Stover et al., Nature 351:456-460 (1991). A wide variety of other vectors useful for therapeutic administration or immunization of the polypeptides of the invention, e.g. adeno and adeno-associated virus vectors, retroviral vectors, Salmonella typhi vectors, detoxified anthrax toxin vectors, and the like, will be apparent to those skilled in the art from the description herein. A preferred vector is Modified Vaccinia Ankara (MVA) (e.g., Bavarian Noridic (MVA-BN)).
- [00229] Standard regulatory sequences well known to those of skill in the art are preferably included in the vector to ensure expression in the human target cells. Several vector elements are desirable: a promoter with a downstream cloning site for polynucleotide, e.g., minigene insertion; a polyadenylation signal for efficient transcription termination; an E. coli origin of replication; and an E. coli selectable marker (e.g. ampicillin or kanamycin resistance). Numerous promoters can be used for this purpose, e.g., the human cytomegalovirus (hCMV) promoter. See, e.g., U.S. Patent Nos. 5,580,859 and 5,589,466 for other suitable promoter sequences. A preferred promoter is the CMV-IE promoter.
- [00230] Polynucleotides, e.g. minigenes, may comprise one or more synthetic or naturallyoccurring introns in the transcribed region. The inclusion of mRNA stabilization sequences and sequences for replication in mammalian cells may also be considered for increasing polynucleotide, e.g. minigene, expression.
- [00231] In addition, the polynucleotide, e.g. minigene, may comprise immunostimulatory sequences (ISSs or CpGs). These sequences may be included in the vector, outside the polynucleotide (e.g. minigene) coding sequence to enhance immunogenicity.
- [00232] In some embodiments, a bi-cistronic expression vector which allows production of both the polynucleotide- (e.g. minigene-) encoded peptides of the invention and a second protein (e.g., one that modulates immunogenicity) can be used. Examples of proteins or

polypeptides that, if co-expressed with peptides of the invention, can enhance an immune response include cytokines (e.g., IL-2, IL-12, GM-CSF), cytokine-inducing molecules (e.g., LeIF), costimulatory molecules, or pan-DR binding proteins (PADRE® molecules, Epimmune, San Diego, CA). Helper T cell (HTL) epitopes such as PADRE® molecules can be joined to intracellular targeting signals and expressed separately from expressed peptides of the invention. Specifically decreasing the immune response by co-expression of immunosuppressive molecules (e.g. TGF-β) may be beneficial in certain diseases.

- [00233] Once an expression vector is selected, the polynucleotide, e.g. minigene, is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate bacterial strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the polynucleotide, e.g. minigene, as well as all other elements included in the vector, are confirmed using restriction mapping, DNA sequence analysis, and/or PCR analysis. Bacterial cells harboring the correct plasmid can be stored as cell banks.
- [00234] Therapeutic/prophylactic quantities of DNA can be produced for example, by fermentation in *E. coli*, followed by purification. Aliquots from the working cell bank are used to inoculate growth medium, and are grown to saturation in shaker flasks or a bioreactor according to well known techniques. Plasmid DNA is purified using standard bioseparation technologies such as solid phase anion-exchange resins available, *e.g.*, from QIAGEN, Inc. (Valencia, California). If required, supercoiled DNA can be isolated from the open circular and linear forms using gel electrophoresis or other methods.
- Purified polynucleotides, e.g. minigenes, can be prepared for injection using a variety of formulations. The simplest of these is reconstitution of lyophilized polynucleotide, e.g. DNA, in sterile phosphate-buffer saline (PBS). This approach, known as "naked DNA," is currently being used for intramuscular (IM) administration in clinical trials. To maximize the immunotherapeutic effects of polynucleotide vaccines, alternative methods of formulating purified plasmid DNA may be used. A variety of such methods have been described, and new techniques may become available. Cationic lipids, glycolipids, and fusogenic liposomes can also be used in the formulation (see, e.g., WO 93/24640; Mannino & Gould-Fogerite, BioTechniques 6(7): 682 (1988); U.S. Patent No. 5,279,833; WO 91/06309; and Felgner, et al., Proc. Nat'l Acad. Sci. USA 84:7413 (1987). In addition, peptides and compounds referred to collectively as protective, interactive, non-condensing compounds (PINC) can also be complexed to purified plasmid DNA to

influence variables such as stability, intramuscular dispersion, or trafficking to specific organs or cell types.

[00236] Known methods in the art can be used to enhance delivery and uptake of a polynucleotide in vivo. For example, the polynucleotide can be complexed to polyvinylpyrrolidone (PVP), to prolong the localized bioavailability of the polynucleotide, thereby enhancing uptake of the polynucleotide by the organisum (see e.g., U.S. Patent No. 6,040,295; EP 0 465 529; WO 98/17814). PVP is a polyamide that is known to form complexes with a wide variety of substances, and is chemically and physiologically inert.

HLA class I presentation of polynucleotide- (e.g. minigene-) encoded peptides. For example, the polynucleotide, e.g. plasmid DNA, is introduced into a mammalian cell line that is a suitable target for standard CTL chromium release assays. The transfection method used will be dependent on the final formulation. For example, electroporation can be used for "naked" DNA, whereas cationic lipids or PVP-formulated DNA allow direct in vitro transfection. A plasmid expressing green fluorescent protein (GFP) can be cotransfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). The transfected cells are then chromium-51 (51Cr) labeled and used as targets for epitope-specific CTLs. Cytolysis of the target cells, detected by 51Cr release, indicates both production and HLA presentation of, polynucleotide-, e.g. minigene-, encoded variants of the invention, or peptides comprising them. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.

[00238] In vivo immunogenicity is a second approach for functional testing of polynucleotides, e.g. minigenes. Transgenic mice expressing appropriate human HLA proteins are immunized with the polynucleotide, e.g. DNA, product. The dose and route of administration are formulation dependent (e.g., IM for polynucleotide (e.g., naked DNA or PVP-formulated DNA) in PBS, intraperitoneal (IP) for lipid-complexed polynucleotide (e.g., DNA)). Eleven to twenty-one days after immunization, splenocytes are harvested and restimulated for one week in the presence of polynucleotides encoding each peptide being tested. Thereafter, for peptides comprising or consisting of variants, standard assays are conducted to determine if there is cytolysis of peptide-loaded, ⁵¹Cr-labeled target cells. Once again, lysis of target cells that were exposed to variants corresponding to those encoded by the polynucleotide (e.g. minigene) demonstrates polynucleotide (e.g., DNA)

vaccine function and induction of CTLs. Immunogenicity of HTL epitopes is evaluated in transgenic mice in an analogous manner.

- [00239] Alternatively, the nucleic acids can be administered using ballistic delivery as described, for instance, in U.S. Patent No. 5,204,253. Using this technique, particles comprised solely of a polynucleotide such as DNA are administered. In a further alternative embodiment for ballistic delivery, polynucleotides such as DNA can be adhered to particles, such as gold particles.
- [00240] The use of polynucleotides such as multi-epitope minigenes is described herein and in, e.g. co-pending application U.S.S.N. 09/311,784; Ishioka et al., J. Immunol. 162:3915-3925, 1999; An, L. and Whitton, J. L., J. Virol. 71:2292, 1997; Thomson, S. A. et al., J. Immunol. 157:822, 1996; Whitton, J. L. et al., J. Virol. 67:348, 1993; Hanke, R. et al., Vaccine 16:426, 1998. For example, a polynucleotide such as a multi-epitope DNA plasmid can be engineered which encodes an epitope derived from multiple regions of a infectious agent (e.g., p53, HER2/nev, MAGE-2/3, or CEA), a pan-DR binding peptide such as the PADRE® universal helper T cell epitope, and an endoplasmic reticulum-translocating signal sequence. As descibed in the sections above, a peptide/polynucleotide may also comprise/encode epitopes that are derived from other infectious agents.
- [00241] Thus, the invention includes peptides as described herein, polynucleotides encoding each of said peptides, as well as compositions comprising the peptides and polynucleotides, and includes methods for producing and methods of using the peptides, polynucleotides, and compositions, as further described below.
- [00242] Compositions. In other embodiments, the invention is directed to a composition comprising one or more peptides and/or polynucleotides of the invention and optionally another component(s).
- In some embodiments, the composition comprises or consists of multiple peptides, e.g., 2, 3, 4, 5, 6, 7, 8, or 9 peptides of the invention. In some embodiments, the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 peptides of the invention. Combinations of peptides include, for example, a peptide comprising or alternatively consisting of the Gag 545 variant EPLTSLKSLF (SEQ ID NO:) and a peptide comprising or alternatively consisting of the Gag 545 variant YPLASLKSLF (SEQ ID NO:), or combinations of peptides from different tables in Tables 6-9 and/or Figures 1A-4.

- [00244] Compositions of the invention may comprise polynucleotides encoding the above peptides and/or combinations of peptides.
- [00245] The composition can comprise at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 peptides and/or polynucleotides selected from those described above or below. At least one of the one or more peptides can be a heteropolymer or a homopolymer. Additionally, the composition can comprise a CTL and/or HTL epitope, which can be derived from a tumor-associated antigen. The additional epitope can also be a PanDR binding molecule, (e.g., a PADRE® universal helper T cell epitope).
- [00246] Optional components include excipients, diluents, proteins such as peptides comprising a CTL epitope, and/or an HTL epitope such as a pan-DR binding peptide (e.g., a PADRE® universal helper T cell epitope), and/or a carrier, polynucleotides encoding such proteins, lipids, or liposomes, as well as other components described herein. There are numerous embodiments of compositions in accordance with the invention, such as a cocktail of one or more peptides and/or polynucleotides (e.g., minigenes); a cocktail of one or more peptides and/or polynucleotides (e.g., minigenes) and one or more CTL and/or HTL epitopes.
- [00247] Compositions may comprise one or more peptides (and/or polynucleotides such as minigenes) of the invention, along with one or more other components as described above and herein. "One or more" refers to any whole unit integer from 1-150, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 peptides, polynucleotides, or other components.
- [00248] Compositions of the invention may be, for example, polynucleotides or polypeptides of the invention combined with or complexed to cationic lipid formulations; lipopeptides (e.g., Vitiello, A. et al., J. Clin. Invest. 95:341, 1995), encapsulated e.g., in poly(DL-lactide-co-glycolide) ("PLG") microspheres (see, e.g., Eldridge, et al., Molec. Immunol. 28:287-294, 1991: Alonso et al., Vaccine 12:299-306, 1994; Jones et al., Vaccine 13:675-681, 1995); peptide compositions contained in immune stimulating complexes (ISCOMS) (see, e.g., Takahashi et al., Nature 344:873-875, 1990; Hu et al., Clin Exp Immunol. 113:235-243, 1998); multiple antigen peptide systems (MAPs) (see e.g., Tam, J. P., Proc. Natl. Acad. Sci. U.S.A. 85:5409-5413, 1988; Tam, J.P., J. Immunol. Methods 196:17-32, 1996); viral, bacterial, or, fungal delivery vectors (Perkus, M. E. et

al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 379, 1996; Chakrabarti, S. et al., Nature 320:535, 1986; Hu, S. L. et al., Nature 320:537, 1986; Kieny, M.-P. et al., AIDS Bio/Technology 4:790, 1986; Top, F. H. et al., J. Infect. Dis. 124:148, 1971; Chanda, P. K. et al., Virology 175:535, 1990); particles of viral or synthetic origin (e.g., Kofler, N. et al., J. Immunol. Methods. 192:25, 1996; Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993; Falo, L. D., Jr. et al., Nature Med. 7:649, 1995); adjuvants (e.g., incomplete Freund's adjuvant) (Warren, H. S., Vogel, F. R., and Chedid, L. A. Annu. Rev. Immunol. 4:369, 1986; Gupta, R. K. et al., Vaccine 11:293, 1993); liposomes (Reddy, R. et al., J. Immunol. 148:1585, 1992; Rock, K. L., Immunol. Today 17:131, 1996); or, particle-absorbed cDNA or other polynucleotides of the invention (Ulmer, J. B. et al., Science 259:1745, 1993; Robinson, H. L., Hunt, L. A., and Webster, R. G., Vaccine 11:957, 1993; Shiver, J. W. et al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 423, 1996; Cease, K. B., and Berzofsky, J. A., Annu. Rev. Immunol. 12:923, 1994 and Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993), etc. Toxintargeted delivery technologies, also known as receptor mediated targeting, such as those of Avant Immunotherapeutics, Inc. (Needham, Massachusetts) or attached to a stress protein, e.g., HSP 96 (Stressgen Biotechnologies Corp., Victoria, BC, Canada) can also be used.

Compositions of the invention comprise polynucleotide-mediated modalities. [00249] DNA or RNA encoding one or more of the peptides of the invention can be administered to a patient. This approach is described, for instance, in Wolff et. al., Science 247:1465 (1990) as well as U.S. Patent Nos. 5,580,859; 5,589,466; 5,804,566; 5,739,118; 5,736,524; 5,679,647; and, WO 98/04720. Examples of DNA-based delivery technologies include "naked DNA", facilitated (bupivicaine, polymers (e.g., PVP, PINC, etc.), peptidemediated) delivery, cationic lipid complexes, and particle-mediated ("gene gun") or pressure-mediated delivery (see, e.g., U.S. Patent No. 5,922,687). Accordingly, peptides of the invention can be expressed by viral or bacterial vectors. Examples of expression vectors include attenuated viral hosts, such as Modified Vaccinia Ankara (MVA) (e.g., Bavarian Noridic), vaccinia or fowlpox. For example, vaccinia virus is used as a vector to express nucleotide sequences that encode the peptides of the invention. Upon introduction into an acutely or chronically infected host or into a non-infected host, the recombinant vaccinia virus expresses the immunogenic peptide, and thereby elicits an immune response. Vaccinia vectors and methods useful in immunization protocols are described in, e.g., U.S. Patent No. 4,722,848. Another vector is BCG (Bacille Calmette Guerin).

BCG vectors are described in Stover et al., Nature 351:456-460 (1991). A wide variety of other vectors useful for therapeutic administration or immunization of the peptides of the invention, e.g. adeno and adeno-associated virus vectors, alpha virus vectors, retroviral vectors, Salmonella typhi vectors, detoxified anthrax toxin vectors, and the like, are apparent to those skilled in the art from the description herein.

- [00250] In certain embodiments, components that induce T cell responses are combined with components that induce antibody responses to the target antigen of interest. A preferred embodiment of such a composition comprises class I and class II epitopes in accordance with the invention. Alternatively, a composition comprises a class I and/or class II epitope in accordance with the invention, along with a PADRE® molecule (Epimmune, San Diego, CA).
- [00251] Compositions of the invention can comprise antigen presenting cells, such as dendritic cells. Antigen presenting cells, e.g., dendritic cells, may be transfected, e.g., with a polynucleotide such as a minigene construct in accordance with the invention, in order to elicit immune responses. The peptide can be bound to an HLA molecule on the antigenresenting cell, whereby when an HLA-restricted cytotoxic T lymphocyte (CTL) is present, a receptor of the CTL binds to a complex of the HLA molecule and the peptide.
- [00252] The compositions of the invention may also comprise antiviral drugs such as interferon-α, or immune adjuvants such as IL-12, GM-CSF, etc.
- [00253] Compositions may comprise an HLA heavy chain, β₂-microglobulin, streptavidin, and/or biotin. The streptavidin may be fluorescently labeled. Compositions may comprise tetramers (see e.g., U.S. Pat. No. 5,635,363; Science 274:94-96 (1996)). A tetramer composition comprising an HLA heavy chain, β₂-microglobulin, streptavidin, and biotin. The streptavidin may be fluorescently labeled. Compositions may also comprise dimers. A dimer composition comprises as MHC molecule and an Ig molecule (see e.g., PNAS 95:7568-73 (1998)).
- In some embodiments it may be desirable to include in the compositions of the invention at least one component which primes cytotoxic T lymphocytes. Lipids have been identified as agents capable of priming CTL in vivo against viral antigens. For example, palmitic acid residues can be attached to the ε-and α- amino groups of a lysine residue and then linked, e.g., via one or more linking residues such as Gly, Gly-Gly-, Ser, Ser-Ser, or the like, to an immunogenic peptide. The lipidated peptide can then be administered either directly in a micelle or particle, incorporated into a liposome, or

emulsified in an adjuvant, e.g., incomplete Freund's adjuvant. A preferred composition comprises palmitic acid attached to ε - and α - amino groups of Lys, which is attached via linkage, e.g., Ser-Ser, to the amino terminus of the peptide.

[00255] As another example of lipid priming of CTL responses, E. coli lipoproteins, such as tripalmitoyl-S-glycerylcysteinlyseryl-serine (P₃CSS) can be used to prime virus specific CTL when covalently attached to an appropriate peptide (see, e.g., Deres, et al., Nature 342:561, 1989). Peptides of the invention can be coupled to P₃CSS, for example, and the lipopeptide administered to an individual to specifically prime a CTL response to the target antigen. Moreover, because the induction of neutralizing antibodies can also be primed with P₃CSS-conjugated epitopes, two such compositions can be combined to more effectively elicit both humoral and cell-mediated responses.

[00256] Another preferred embodiment is a composition comprising one or more peptides of the invention emulsified in IFA.

[00257] Compositions of the invention may also comprise CTL and/or HTL peptides. Such CTL and HTL peptides can be modified by the addition of amino acids to the termini of a peptide to provide for ease of linking peptides one to another, for coupling to a carrier support or larger peptide, for modifying the physical or chemical properties of the peptide or oligopeptide, or the like. Amino acids such as tyrosine, cysteine, lysine, glutamic or aspartic acid, or naturally or unnaturally occuring amino acid residues, can be introduced at the carboxyl- or amino-terminus of the peptide or oligopeptide, particularly class I peptides. However, it is to be noted that modification at the carboxyl terminus of a CTL epitope may, in some cases, alter binding characteristics of the peptide. In addition, the peptide or oligopeptide sequences can differ from the natural sequence by being modified by terminal-NH2 acylation, e.g., by alkanoyl (C1-C20) or thioglycolyl acetylation, terminalcarboxyl amidation, e.g., ammonia, methylamine, etc. In some instances these modifications may provide sites for linking to a support or other molecule. CTL and HTL epitopes may comprise additional amino acids, such as those described above including spacers.

[00258] A further embodiment of a composition in accordance with the invention is an antigen presenting cell that comprises one or more peptides in accordance with the invention. The antigen presenting cell can be a "professional" antigen presenting cell, such as a dendritic cell. The antigen presenting cell can comprise the peptide of the invention by any means known or to be determined in the art. Such means include pulsing

of dendritic cells with one or more individual peptides, by nucleic acid administration such as ballistic nucleic acid delivery or by other techniques in the art for administration of nucleic acids, including vector-based, e.g. viral vector, delivery of nucleic acids.

- [00259] Compositions may comprise carriers. Carriers that can be used with compositions of the invention are well known in the art, and include, e.g., thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly L-lysine, poly L-glutamic acid, influenza virus proteins, hepatitis B virus core protein, and the like.
- [00260] The compositions (e.g. pharmaceutical compositions) can contain a physiologically tolerable diluent such as water, or a saline solution, preferably phosphate buffered saline. Additionally, as disclosed herein, CTL responses can be primed by conjugating peptides of the invention to lipids, such as tripalmitoyl-S-glyceryl-cysteinyl-seryl-serine (P₃CSS).
- [00261] Compositions of the invention may be pharmaceutically acceptable compositions. Pharmaceutical compositions preferably contain an immunologically effective amount of one or more peptides and/or polynucleotides of the invention, and optionally one or more other components which are pharmaceutically acceptable. A preferred composition comprises one or more peptides of the invention and IFA. A more preferred composition of the invention comprises one or more peptides of the invention, one or more peptides, and IFA.
- [00262] Upon immunization with a peptide and/or polynucleotide and/or composition in accordance with the invention, via injection (e.g., SC, ID, IM), aerosol, oral, transdermal, transmucosal, intrapleural, intrathecal, or other suitable routes, the immune system of the host responds to the vaccine by an immune response comprising the production of antibodies, CTLs and/or HTLs specific for the desired antigen(s). Consequently, the host becomes at least partially immune to subsequent exposure to the infectious agent(s), or at least partially resistant to further development of infectious agent-bearing cells and thereby derives a prophylactic or therapeutic benefit.
- [00263] Furthermore, the peptides, primers, and epitopes of the invention can be used in any desired immunization or administration regimen; e.g., as part of periodic vaccinations such as annual vaccinations as in the veterinary arts or as in periodic vaccinations as in the human medical arts, or as in a prime-boost regime wherein an inventive vector or recombinant is administered either before or after the administration of the same or of a different epitope of interest or recombinant or vector expressing such as a same or different epitope of interest (including an inventive recombinant or vector expressing such

as a same or different epitope of interest), see, e.g., U.S. Pat. Nos. 5,997,878; 6,130,066; 6,180,398; 6,267,965; and 6,348,450. An useful viral vector of the present invention is Modified Vaccinia Ankara (MVA) (e.g., Bavarian Noridic (MVA-BN)).

Recent studies have indicated that a prime-boost protocol, whereby immunization [00264] with a poxvirus recombinant expressing a foreign gene product is followed by a boost using a purified subunit preparation form of that gene product, elicits an enhanced immune response relative to the response elicited with either product alone. Human volunteers immunized with a vaccinia recombinant expressing the HIV-1 envelope glycoprotein and boosted with purified HIV-1 envelope glycoprotein subunit preparation exhibit higher HIV-1 neutralizing antibody titers than individuals immunized with just the vaccinia recombinant or purified envelope glycoprotein alone (Graham et al., J. Infect. Dis., 167:533-537 (1993); Cooney et al., Proc. Natl. Acad. Sci. USA, 90:1882-1886 (1993)). Humans immunized with two injections of an ALVAC-HIV-1 env recombinant (vCP125) failed to develop HIV specific antibodies. Boosting with purified rgp160 from a vaccinia virus recombinant resulted in detectable HIV-1 neutralizing antibodies. Furthermore, specific lymphocyte T cell proliferation to rgp160 was clearly increased by the boost with rgp160. Envelope specific cytotoxic lymphocyte activity was also detected with this vaccination regimen (Pialoux et al., AIDS Res. and Hum. Retroviruses, 11:272-381 (1995)). Macaques immunized with a vaccinia recombinant expressing the simian immunodeficiency virus (SIV) envelope glycoprotein and boosted with SIV envelope glycoprotein from a baculovirus recombinant are protected against SIV challenge (Hu et al., AID Res. and Hum. Retroviruses, 3:615-620 (1991); Hu et al., Science 255:456-459 (1992)). In the same fashion, purified HCMVgB protein can be used in prime-boost protocols with NYVAC or ALVAC-gB recombinants.

[00265] In certain embodiments, the polynucleotides are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA 84:74137416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA 86:60776081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol.

Chem. 265:1018910192 (1990), which is herein incorporated by reference), in functional form.

[00266] Cationic liposomes are readily available. For example, N-[12,3-dioleyloxy)-propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA 84:74137416 (1987)). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[00267] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:74137417. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[00268] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[00269] For example, commercially available dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar [00270] vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology 101:512527 (1983). For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca2+-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta 394:483 (1975); Wilson et al., Cell 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reversephase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); SchaeferRidder et al., Science 215:166 (1982)).

[00271] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[00272] U.S. Patent No. 5,676,954 reports on the injection of genetic material, complexed with cationic liposome carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

Binding Affinity of Variants for HLA Molecules

[00273] As indicated herein, the large degree of HLA polymorphism is an important factor to be taken into account with the epitope-based approach to developing therapeutics and diagnostics. To address this factor, epitope selection encompassing identification of peptides capable of binding at high or intermediate affinity to multiple HLA molecules is preferably utilized, most preferably these epitopes bind at high or intermediate affinity to two or more allele-specific HLA molecules. However, in some embodiments, it is preferred that all epitopes in a given composition bind to the alleles of a single HLA supertype or a single HLA molecule.

Variants of the invention preferably include those that have an IC₅₀ or binding affinity value for a class I HLA molecule(s) of 500 nM or better (i.e., the value is \leq 500 nM). In certain embodiments of the invention, peptides of interest have an IC₅₀ or binding affinity value for a class I HLA molecule(s) of 200 nM or better. In certain embodiments of the invention, peptides of interest, such as A1 and A24 peptides, have an IC₅₀ or binding affinity value for a class I HLA molecule(s) of 100 nM or better. If HTL epitopes are included, they preferably are HTL epitopes that have an IC₅₀ or binding affinity value for class II HLA molecules of 1000 nM or better, (i.e., the value is \leq 1,000 nM). For example, peptide binding is assessed by testing the capacity of a candidate peptide to bind to a purified HLA molecule in vitro. Peptides exhibiting high or intermediate affinity are then considered for further analysis. Selected peptides are generally tested on other members of the supertype family. In preferred embodiments, peptides that exhibit cross-reactive binding are then used in cellular screening analyses or vaccines.

[00275] The relationship between binding affinity for HLA class I molecules and immunogenicity of discrete peptide epitopes on bound antigens was determined for the first time by inventors at Epimmune. As disclosed in greater detail herein, higher HLA binding affinity is correlated with greater immunogenicity.

[00276] Greater immunogenicity can be manifested in several different ways. Immunogenicity corresponds to whether an immune response is elicited at all, and to the vigor of any particular response, as well as to the extent of a population in which a response is elicited. For example, a peptide might elicit an immune response in a diverse array of the population, yet in no instance produce a vigorous response. In accordance

with these principles, close to 90% of high binding peptides have been found to elicit a response and thus be "immunogenic," as contrasted with about 50% of the peptides that bind with intermediate affinity. (See, e.g., Schaeffer et al. PNAS (1988)) High affinity-binding class I peptides generally have an affinity of less than or equal to 100 nM. Moreover, not only did peptides with higher binding affinity have an enhanced probability of generating an immune response, the generated response tended to be more vigorous than the response seen with weaker binding peptides. As a result, less peptide is required to elicit a similar biological effect if a high affinity binding peptide is used rather than a lower affinity one. Thus, in some preferred embodiments of the invention, high affinity binding epitopes are used.

[00277] The correlation between binding affinity and immunogenicity was analyzed by the present inventors by two different experimental approaches (see, e.g., Sette, et al., J. Immunol. 153:5586-5592 (1994)). In the first approach, the immunogenicity of potential epitopes ranging in HLA binding affinity over a 10,000-fold range was analyzed in HLA-A*0201 transgenic mice. In the second approach, the antigenicity of approximately 100 different hepatitis B virus (HBV)-derived potential epitopes, all carrying A*0201 binding motifs, was assessed by using PBL from acute hepatitis patients. Pursuant to these approaches, it was determined that an affinity threshold value of approximately 500 nM (preferably 50 nM or less) determines the capacity of a peptide epitope to elicit a CTL response. These data are true for class I binding affinity measurements for naturally processed peptides and for synthesized T cell epitopes. These data also indicate the important role of determinant selection in the shaping of T cell responses (see, e.g., Schaeffer et al. Proc. Natl. Acad. Sci. USA 86:4649-4653 (1989)).

II (i.e., HLA DR) molecules has also been delineated (see, e.g., Southwood et al. J. Immunology 160:3363-3373 (1998), and U.S. Patent No. 6,413,527, issued July 2, 2002). In order to define a biologically significant threshold of HLA class II binding affinity, a database of the binding affinities of 32 DR-restricted epitopes for their restricting element (i.e., the HLA molecule that binds the epitope) was compiled. In approximately half of the cases (15 of 32 epitopes), DR restriction was associated with high binding affinities, i.e. binding affinity values of 100 nM or less. In the other half of the cases (16 of 32), DR restriction was associated with intermediate affinity (binding affinity values in the 100-1000 nM range). In only one of 32 cases was DR restriction associated with an IC50

of 1000 nM or greater. Thus, 1000 nM is defined as an affinity threshold associated with immunogenicity in the context of DR molecules.

[00279] The binding affinity of peptides for HLA molecules can be determined as described in Example 1, below.

Enhancing Population Coverage of the Vaccine

[00280] The primary anchor residues of the HLA class I peptide epitope supermotifs and motifs are summarized in Tables 1-2. Allele-specific HLA molecules that are comprised by the various HLA class I supertypes are listed in Table 4. In some cases, patterns of amino acid residues are present in both a motif and a supermotif. The relationship of a particular motif and any related supermotif is indicated in the description of the individual motifs.

[00281] By inclusion of one or more epitopes from several motifs or supermotifs in a vaccine composition, enhanced population coverage for major global ethnicities can be obtained.

Assays to Detect T-Cell Responses

[00282] Once HLA binding peptides are identified, they can be tested for the ability to elicit a T-cell response. The preparation and evaluation of motif-bearing peptides are described, e.g., in PCT publications WO 94/20127 and WO 94/03205. Briefly, peptides comprising epitopes from a particular antigen are synthesized and tested for their ability to bind to relevant HLA proteins. These assays may involve evaluation of peptide binding to purified HLA class I molecules in relation to the binding of a radioiodinated reference peptide. Alternatively, cells expressing empty class I molecules (i.e. cell surface HLA molecules that lack any bound peptide) may be evaluated for peptide binding by immunofluorescent staining and flow microfluorimetry. Other assays that may be used to evaluate peptide binding include peptide-dependent class I assembly assays and/or the inhibition of CTL recognition by peptide competition. Those peptides that bind to an HLA class I molecule, typically with an affinity of 500 nM or less, are further evaluated for their ability to serve as targets for CTLs derived from infected or immunized individuals, as well as for their capacity to induce primary in vitro or in vivo CTL

responses that can give rise to CTL populations capable of reacting with selected target cells associated with pathology.

[00283] Analogous assays are used for evaluation of HLA class II binding peptides. HLA class II motif-bearing peptides that are shown to bind, typically at an affinity of 1000 nM or less, are further evaluated for the ability to stimulate HTL responses.

Conventional assays utilized to detect T cell responses include proliferation assays, [00284] lymphokine secretion assays, direct cytotoxicity assays, and limiting dilution assays. For example, antigen-presenting cells that have been incubated with a peptide can be assayed for the ability to induce CTL responses in responder cell populations. Antigen-presenting cells can be normal cells such as peripheral blood mononuclear cells or dendritic cells. Alternatively, mutant, non-human mammalian cell lines that have been transfected with a human class I MHC gene, and that are deficient in their ability to load class I molecules with internally processed peptides, are used to evaluate the capacity of the peptide to induce in vitro primary CTL responses. Peripheral blood mononuclear cells (PBMCs) can be used as the source of CTL precursors. Antigen presenting cells are incubated with peptide, after which the peptide-loaded antigen-presenting cells are then incubated with the responder cell population under optimized culture conditions. Positive CTL activation can be determined by assaying the culture for the presence of CTLs that lyse radio-labeled target cells, either specific peptide-pulsed targets or target cells that express endogenously processed antigen from which the specific peptide was derived. Alternatively, the presence of epitope-specific CTLs can be determined by IFNy in situ ELISA.

[00285] In an embodiment of the invention, directed to diagnostics, a method has been devised which allows direct quantification of antigen-specific T cells by staining with fluorescein-labelled HLA tetrameric complexes (Altman, J. D. et al., Proc. Natl. Acad. Sci. USA 90:10330, 1993; Altman, J. D. et al., Science 274:94, 1996). Other options include staining for intracellular lymphokines, and interferon release assays or ELISPOT assays. Tetramer staining, intracellular lymphokine staining and ELISPOT assays all appear to be at least 10-fold more sensitive than more conventional assays (Lalvani, A. et al., J. Exp. Med. 186:859, 1997; Dunbar, P. R. et al., Curr. Biol. 8:413, 1998; Murali-Krishna, K. et al., Immunity 8:177, 1998). Additionally, DimerX technology can be used as a means of quantitation (see, e.g., Science 274:94-99 (1996) and Proc. Natl. Acad. Sci. 95:7568-73 (1998)).

- [00286] HTL activation may also be assessed using techniques known to those in the art, such as T cell proliferation or lymphokine secretion (see, e.g. Alexander et al., Immunity 1:751-761, 1994).
- [00287] Alternatively, immunization of HLA transgenic mice can be used to determine immunogenicity of peptide epitopes. Several transgenic mouse strains, e.g., mice with human A2.1, A11 (which can additionally be used to analyze HLA-A3 epitopes), and B7 alleles have been characterized. Other transgenic mice strains (e.g., transgenic mice for HLA-A1 and A24) are being developed. Moreover, HLA-DR1 and HLA-DR3 mouse models have been developed. In accordance with principles in the art, additional transgenic mouse models with other HLA alleles are generated as necessary.
- [00288] Such mice can be immunized with peptides emulsified in Incomplete Freund's Adjuvant; thereafter any resulting T cells can be tested for their capacity to recognize target cells that have been peptide-pulsed or transfected with genes encoding the peptide of interest. CTL responses can be analyzed using cytotoxicity assays described above. Similarly, HTL responses can be analyzed using, e.g., T cell proliferation or lymphokine secretion assays.

Minigenes

- of multiple epitopes. Nucleic acids encoding multiple epitopes are a useful embodiment of the invention; discrete peptide epitopes or polyepitopic peptides can be encoded. The epitopes to be included in a minigene are preferably selected according to the guidelines set forth in the previous section. Examples of amino acid sequences that can be included in a minigene include: HLA class I epitopes, HLA class II epitopes, a ubiquitination signal sequence, and/or a targeting sequence such as an endoplasmic reticulum (ER) signal sequence to facilitate movement of the resulting peptide into the endoplasmic reticulum. Examples of minigene constructs are shown in Tables 23-28.
- [00290] The use of multi-epitope minigenes is also described in, e.g., co-pending applications U.S.S.N. 09/311,784, 09/894,018, 60/419,973, 60/415,463; Ishioka et al., J. Immunol. 162:3915-3925, 1999; An, L. and Whitton, J. L., J. Virol. 71:2292, 1997; Thomson, S. A. et al., J. Immunol. 157:822, 1996; Whitton, J. L. et al., J. Virol. 67:348, 1993; Hanke, R. et al., Vaccine 16:426, 1998. For example, a multi-epitope DNA plasmid

encoding nine dominant HLA-A*0201- and A11-restricted CTL epitopes derived from the polymerase, envelope, and core proteins of HBV and human immunodeficiency virus (HIV), a PADRE® universal helper T cell (HTL) epitope, and an endoplasmic reticulum-translocating signal sequence has been engineered. Immunization of HLA transgenic mice with this plasmid construct resulted in strong CTL induction responses against the nine CTL epitopes tested. This CTL response was similar to that observed with a lipopeptide of known immunogenicity in humans, and significantly greater than immunization using peptides in oil-based adjuvants. Moreover, the immunogenicity of DNA-encoded epitopes in vitro was also correlated with the in vitro responses of specific CTL lines against target cells transfected with the DNA plasmid. These data show that the minigene served: 1.) to generate a CTL response and 2.) to generate CTLs that recognized cells expressing the encoded epitopes. A similar approach can be used to develop minigenes encoding epitopes of an infectious agent.

for example, to create a DNA sequence encoding the selected epitopes (minigene) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated. A human codon usage table can be used to guide the codon choice for each amino acid. These epitope-encoding DNA sequences may be directly adjoined, so that when translated, a continuous peptide sequence is created. However, to optimize expression and/or immunogenicity, additional elements can be incorporated into the minigene design such as spacer amino acid residues between epitopes. HLA presentation of CTL and HTL epitopes may be improved by including synthetic (e.g. poly-alanine) or naturally-occurring flanking sequences adjacent to the CTL or HTL epitopes; these larger peptides comprising the epitope(s) are within the scope of the invention. In one embodiment, spacer amino acid residues between one or more CTL and/or HTL epitopes are designed so as to minimize junctional epitopes that may result from the juxtaposition of 2 CTL and/or HTL epitopes.

[00292] The minigene sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the minigene. Overlapping oligonucleotides (30-100 bases long) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. This synthetic minigene, encoding the epitope peptide, can then be cloned into a desired expression vector.

[00293] Standard regulatory sequences well known to those of skill in the art are preferably included in the vector to ensure expression in the target cells. Several vector elements are desirable: a promoter with a downstream cloning site for minigene insertion; a polyadenylation signal for efficient transcription termination; an *E. coli* origin of replication; and an *E. coli* selectable marker (e.g. ampicillin or kanamycin resistance). Numerous promoters can be used for this purpose, e.g., the human cytomegalovirus (hCMV) CMV-IE promoter. See, e.g., U.S. Patent Nos. 5,580,859 and 5,589,466 for other suitable promoter sequences.

[00294] Optimized peptide expression and immunogenicity can be achieved by certain modifications to a minigene construct. For example, in some cases introns facilitate efficient gene expression, thus one or more synthetic or naturally-occurring introns can be incorporated into the transcribed region of the minigene. The inclusion of mRNA stabilization sequences and sequences for replication in mammalian cells may also be considered for increasing minigene expression.

[00295] Once an expression vector is selected, the minigene is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate bacterial strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the minigene, as well as all other elements included in the vector, are confirmed using restriction mapping, PCR and/or DNA sequence analysis. Bacterial cells harboring the correct plasmid can be stored as cell banks.

[00296] In addition, immunostimulatory sequences (ISSs or CpGs) appear to play a role in the immunogenicity of DNA vaccines. These sequences may be included in the vector, outside the minigene coding sequence to enhance immunogenicity.

In some embodiments, a bi-cistronic expression vector which allows production of both the minigene-encoded epitopes and a second protein (e.g., one that modulates immunogenicity) can be used. Examples of proteins or polypeptides that, if co-expressed with epitopes, can enhance an immune response include cytokines (e.g., IL-2, IL-12, GM-CSF), cytokine-inducing molecules (e.g., LeIF), costimulatory molecules, or pan-DR binding proteins (PADRE®, Epimmune, San Diego, CA). Helper T cell (HTL) epitopes such as PADRE® molecules can be joined to intracellular targeting signals and expressed separately from expressed CTL epitopes. This can be done in order to direct HTL epitopes to a cell compartment different than that of the CTL epitopes, one that provides for more efficient entry of HTL epitopes into the HLA class II pathway, thereby

improving HTL induction. In contrast to HTL or CTL induction, specifically decreasing the immune response by co-expression of immunosuppressive molecules (e.g. $TGF-\beta$) may be beneficial in certain diseases.

- [00298] Therapeutic quantities of plasmid DNA can be produced for example, by fermentation in *E. coli*, followed by purification. Aliquots from the working cell bank are used to inoculate growth medium, and are grown to saturation in shaker flasks or a bioreactor according to well known techniques. Plasmid DNA is purified using standard bioseparation technologies such as solid phase anion-exchange resins available, *e.g.*, from QIAGEN, Inc. (Valencia, California). If required, supercoiled DNA can be isolated from the open circular and linear forms using gel electrophoresis or other methods.
- [00299] Purified plasmid DNA can be prepared for injection using a variety of The simplest of these is reconstitution of lyophilized DNA in sterile formulations. phosphate-buffer saline (PBS). This approach, known as "naked DNA," is currently being used for intramuscular (IM) administration in clinical trials. To maximize the immunotherapeutic effects of minigene vaccines, alternative methods of formulating purified plasmid DNA may be used. A variety of such methods have been described, and new techniques may become available. Cationic lipids, glycolipids, and fusogenic liposomes can also be used in the formulation (see, e.g., WO 93/24640; Mannino & Gould-Fogerite, BioTechniques 6(7): 682 (1988); U.S. Patent No. 5,279,833; WO 91/06309; and Felgner, et al., Proc. Nat'l Acad. Sci. USA 84:7413 (1987). In addition, peptides and compounds referred to collectively as protective, interactive, non-condensing compounds (PINC) can also be complexed to purified plasmid DNA to influence variables such as stability, intramuscular dispersion, or trafficking to specific organs or cell types.
- [00300] Known methods in the art can be used to enhance delivery and uptake of a polynucleotide in vivo. For example, the polynucleotide can be complexed to polyvinylpyrrolidone (PVP), to prolong the localized bioavailability of the polynucleotide, thereby enhancing uptake of the polynucleotide by the organisum (see e.g., U.S. Patent No. 6,040,295; EP 0 465 529; WO 98/17814). PVP is a polyamide that is known to form complexes with a wide variety of substances, and is chemically and physiologically inert.
- [00301] Target cell sensitization can be used as a functional assay of the expression and HLA class I presentation of minigene-encoded epitopes. For example, the plasmid DNA is introduced into a mammalian cell line that is a suitable target for standard CTL chromium release assays. The transfection method used will be dependent on the final

formulation, electroporation can be used for "naked" DNA, whereas cationic lipids or DNA:PVP compositions allow direct *in vitro* transfection. A plasmid expressing green fluorescent protein (GFP) can be co-transfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). The transfected cells are then chromium-51 (⁵¹Cr) labeled and used as targets for epitope-specific CTLs. Cytolysis of the target cells, detected by ⁵¹Cr release, indicates both the production and HLA presentation of, minigene-encoded CTL epitopes. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.

[00302] In vivo immunogenicity is a second approach for functional testing of minigene DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product. The dose and route of administration are formulation dependent (e.g., IM for DNA in PBS, intraperitoneal (IP) for lipid-complexed DNA). Eleven to twenty-one days after immunization, splenocytes are harvested and restimulated for one week in the presence of peptides encoding each epitope being tested. Thereafter, for CTLs, standard assays are conducted to determine if there is cytolysis of peptide-loaded, ⁵¹Cr-labeled target cells. Once again, lysis of target cells that were exposed to epitopes corresponding to those in the minigene, demonstrates DNA vaccine function and induction of CTLs. Immunogenicity of HTL epitopes is evaluated in transgenic mice in an analogous manner.

[00303] Alternatively, the nucleic acids can be administered using ballistic delivery as described, for instance, in U.S. Patent No. 5,204,253. Using this technique, particles comprised solely of DNA are administered. In a further alternative embodiment for ballistic delivery, DNA can be adhered to particles, such as gold particles.

Vaccine Compositions

[00304] Vaccines that contain an immunologically effective amount of one or more peptides or polynucleotides of the invention are a further embodiment of the invention. The peptides can be delivered by various means or formulations, all collectively referred to as "vaccine" compositions. Such vaccine compositions, and/or modes of administration, can include, for example, naked DNA, DNA formulated with PVP, DNA in cationic lipid formulations; lipopeptides (e.g., Vitiello, A. et al., J. Clin. Invest. 95:341, 1995), DNA or peptides, encapsulated e.g., in poly(DL-lactide-co-glycolide) ("PLG") microspheres (see, e.g., Eldridge, et al., Molec. Immunol. 28:287-294, 1991: Alonso et al.,

Vaccine 12:299-306, 1994; Jones et al., Vaccine 13:675-681, 1995); peptide compositions contained in immune stimulating complexes (ISCOMS) (see, e.g., Takahashi et al., Nature 344:873-875, 1990; Hu et al., Clin Exp Immunol. 113:235-243, 1998); multiple antigen peptide systems (MAPs) (see e.g., Tam, J. P., Proc. Natl. Acad. Sci. U.S.A. 85:5409-5413, 1988; Tam, J.P., J. Immunol. Methods 196:17-32, 1996); viral, bacterial, or, fungal delivery vectors (Perkus, M. E. et al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 379, 1996; Chakrabarti, S. et al., Nature 320:535, 1986; Hu, S. L. et al., Nature 320:537, 1986; Kieny, M.-P. et al., AIDS Bio/Technology 4:790, 1986; Top, F. H. et al., J. Infect. Dis. 124:148, 1971; Chanda, P. K. et al., Virology 175:535, 1990); particles of viral or synthetic origin (e.g., Kosler, N. et al., J. Immunol. Methods. 192:25, 1996; Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993; Falo, L. D., Jr. et al., Nature Med. .7:649, 1995); adjuvants (e.g., incomplete freund's advjuvant) (Warren, H. S., Vogel, F. R., and Chedid, L. A. Annu. Rev. Immunol. 4:369, 1986; Gupta, R. K. et al., Vaccine 11:293, 1993); liposomes (Reddy, R. et al., J. Immunol. 148:1585, 1992; Rock, K. L., Immunol. Today 17:131, 1996); or, particle-absorbed DNA (Ulmer, J. B. et al., Science 259:1745, 1993; Robinson, H. L., Hunt, L. A., and Webster, R. G., Vaccine 11:957, 1993; Shiver, J. W. et al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 423, 1996; Cease, K. B., and Berzofsky, J. A., Annu. Rev. Immunol. 12:923, 1994 and Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993), etc. Toxin-targeted delivery technologies, also known as receptor mediated targeting, such as those of Avant Immunotherapeutics, Inc. (Needham, Massachusetts) or attached to a stress protein, e.g., HSP 96 (Stressgen Biotechnologies Corp., Victoria, BC, Canada) can also be used.

[00305] Vaccines of the invention comprise nucleic acid mediated modalities. DNA or RNA encoding one or more of the peptides of the invention can be administered to a patient. This approach is described, for instance, in Wolff et. al., Science 247:1465 (1990) as well as U.S. Patent Nos. 5,580,859; 5,589,466; 5,804,566; 5,739,118; 5,736,524; 5,679,647; and, WO 98/04720. Examples of DNA-based delivery technologies include "naked DNA", facilitated (bupivicaine, polymers (e.g., PVP), peptide-mediated) delivery, cationic lipid complexes, and particle-mediated ("gene gun") or pressure-mediated delivery (see, e.g., U.S. Patent No. 5,922,687). Accordingly, peptide vaccines of the invention can be expressed by viral or bacterial vectors. Examples of expression vectors include attenuated viral hosts, such as vaccinia or fowlpox. For example, vaccinia virus is used as a vector to express nucleotide sequences that encode the peptides of the invention

(e.g., MVA). Upon introduction into an acutely or chronically infected host or into a non-infected host, the recombinant vaccinia virus expresses the immunogenic peptide, and thereby elicits an immune response. Vaccinia vectors and methods useful in immunization protocols are described in, e.g., U.S. Patent No. 4,722,848. Another vector is BCG (Bacille Calmette Guerin). BCG vectors are described in Stover et al., Nature 351:456-460 (1991). A wide variety of other vectors useful for therapeutic administration or immunization of the peptides of the invention, e.g. adeno and adeno-associated virus vectors, alpha virus vectors, retroviral vectors, Salmonella typhi vectors, detoxified anthrax toxin vectors, and the like, are apparent to those skilled in the art from the description herein.

[00306] Furthermore, vaccines in accordance with the invention can comprise one or more peptides of the invention. Accordingly, a peptide can be present in a vaccine individually; alternatively, the peptide can exist as a homopolymer comprising multiple copies of the same peptide, or as a heteropolymer of various peptides. Polymers have the advantage of increased probability for immunological reaction and, where different peptide epitopes are used to make up the polymer, the ability to induce antibodies and/or T cells that react with different antigenic determinants of the antigen targeted for an immune response. The composition may be a naturally occurring region of an antigen or can be prepared, e.g., recombinantly or by chemical synthesis.

[00307] Carriers that can be used with vaccines of the invention are well known in the art, and include, e.g., thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly L-lysine, poly L-glutamic acid, influenza virus proteins, hepatitis B virus core protein, and the like. The vaccines can contain a physiologically tolerable diluent such as water, or a saline solution, preferably phosphate buffered saline. Generally, the vaccines also include an adjuvant. Adjuvants such as incomplete Freund's adjuvant, aluminum phosphate, aluminum hydroxide, or alum are examples of materials well known in the art. Additionally, as disclosed herein, CTL responses can be primed by conjugating peptides of the invention to lipids, such as tripalmitoyl-S-glyceryl-cysteinyl-seryl-serine (P₃CSS).

[00308] Upon immunization with a peptide composition in accordance with the invention, via injection (e.g., SC, ID, IM), aerosol, oral, transdermal, transmucosal, intrapleural, intrathecal, or other suitable routes, the immune system of the host responds to the vaccine by producing antibodies, CTLs and/or HTLs specific for the desired antigen.

Consequently, the host becomes at least partially immune to subsequent exposure to the infectious agent, and thereby derives a prophylactic or therapeutic benefit.

- [00309] In certain embodiments, components that induce T cell responses are combined with components that induce antibody responses to the target antigen of interest. A preferred embodiment of such a composition comprises class I and class II epitopes in accordance with the invention. Alternatively, a composition comprises a class I and/or class II epitope in accordance with the invention, along with a PADRE® molecule (Epimmune, San Diego, CA).
- [00310] Vaccines of the invention can comprise antigen presenting cells, such as dendritic cells, as a vehicle to present peptides of the invention. For example, dendritic cells are transfected, e.g., with a minigene construct in accordance with the invention, in order to elicit immune responses. Minigenes are discussed in greater detail in a following section. Vaccine compositions can be created in vitro, following dendritic cell mobilization and harvesting, whereby loading of dendritic cells occurs in vitro.
- [00311] The vaccine compositions of the invention may also be used in combination with antiviral drugs such as interferon-α, or immune adjuvants such as IL-12, GM-CSF, etc.
- [00312] Preferably, the following principles are utilized when selecting epitope(s) and/or analogs for inclusion in a vaccine, either peptide-based or nucleic acid-based formulations. Exemplary variants that may be utilized in a vaccine to treat or prevent infectious agent-mediated disease are set out in Tables 6-9 and Figures 1A-4. Each of the following principles can be balanced in order to make the selection. When multiple epitopes are to be used in a vaccine, the epitopes may be, but need not be, contiguous in sequence in the native antigen from which the epitopes are derived. Such multiple epitotes can refer to the order of epitopes within a peptide, or to the selection of epitopes that come from the same reagion, for use in either individual peptides or in a multi-epitopic peptide.
 - 1.) Variants are selected which, upon administration, mimic immune responses that have been observed to be correlated with prevention or clearance of infectious disease. For HLA Class I, this generally includes 3-7 variants from at least one infectious agent or antigen thereof.
 - 2.) Variants are selected that have the requisite binding affinity established to be correlated with immunogenicity: for HLA Class I an IC₅₀ of 500 nM or less, or for Class II an IC₅₀ of 1000 nM or less. For HLA Class I it is presently preferred to select a peptide having an IC₅₀ of 200 nM or less, as this is believed to better correlate not only to induction of an immune response, but to *in vitro* tumor cell killing as well. For HLA A1 and A24, it is especially preferred to select a peptide having an IC₅₀ of 100 nM or less.

- 3.) Supermotif bearing-variants, or a sufficient array of allele-specific motif-bearing variants, are selected to give broad population coverage. In general, it is preferable to have at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art, can be employed to assess the breadth of population coverage.
- 4.) Of particular relevance are "nested epitopes." Nested epitopes occur where at least two epitopes overlap in a given peptide sequence. For example, a nested epitope can be a fragment of an antigen from a region that contains multiple epitopes that are overleapping, or one epitope that is completely encompassed by another, e.g., A2 peptides MAGE3.159 and MAGE3.160 are nested epitopes. A peptide comprising "transcendent nested epitopes" is a peptide that has both HLA class I and HLA class II epitopes in it. When providing nested epitopes, it is preferable to provide a sequence that has the greatest number of epitopes per provided sequence. Preferably, one avoids providing a peptide that is any longer than the amino terminus of the amino terminal epitope and the carboxyl terminus of the carboxyl terminal epitope in the peptide. When providing a sequence comprising nested epitopes, it is important to evaluate the sequence in order to insure that it does not have pathological or other deleterious biological properties; this is particularly relevant for vaccines directed to infectious organisms.
- 5.) If a protein with multiple epitopes or a polynucleotide (e.g., minigene) is created, an objective is to generate the smallest peptide that encompasses the epitopes of interest. This principle is similar, if not the same as that employed when selecting a peptide comprising nested epitopes. However, with an artificial peptide comprising multipe epitopes, the size minimization objective is balanced against the need to integrate any spacer sequences between epitopes in the polyepitopic protein. Spacer amino acid residues can be introduced to avoid junctional epitopes (an epitope recognized by the immune system, not present in the target antigen, and only created by the man-made juxtaposition of epitopes), or to facilitate cleavage between epitopes and thereby enhance epitope presentation. Junctional epitopes are generally to be avoided because the recipient may generate an immune response to that non-native epitope. Of particular concern is a junctional epitope that is a "dominant epitope." A dominant epitope may lead to such a zealous response that immune responses to other epitopes are diminished or suppressed.
- [00313] The principles are the same, except junctional epitopes applies to the sequences surrounding the epitope. One must also take care with other sequences in construct to avoid immune response.

T CELL PRIMING MATERIALS

[00314] In some embodiments it may be desirable to include in the pharmaceutical compositions of the invention at least one component which primes cytotoxic T

lymphocytes. Lipids have been identified as agents capable of facilitating the priming in vitro CTL response against viral antigens. For example, palmitic acid residues can be attached to the ε -and α - amino groups of a lysine residue and then linked to an immunogenic peptide. One or more linking moieties can be used such as Gly, Gly-Gly-, Ser, Ser-Ser, or the like. The lipidated peptide can then be administered directly in a micelle or particle, incorporated into a liposome, or emulsified in an adjuvant, e.g., incomplete Freund's adjuvant. A preferred immunogenic composition comprises palmitic acid attached to ε - and α - amino groups of Lys via a linking moiety, e.g., Ser-Ser, added to the amino terminus of an immunogenic peptide.

[00315] In another embodiment of lipid-facilitated priming of CTL responses, E. coli lipoproteins, such as tripalmitoyl-S-glyceryl-cysteinyl-seryl-serine (P₃CSS) can be used to prime CTL when covalently attached to an appropriate peptide. (See, e.g., Deres, et al., Nature 342:561, 1989). Thus, peptides of the invention can be coupled to P₃CSS, and the lipopeptide administered to an individual to specifically prime a CTL response to the target antigen. Moreover, because the induction of neutralizing antibodies can also be primed with P₃CSS-conjugated epitopes, two such compositions can be combined to elicit both humoral and cell-mediated responses.

DENDRITIC CELLS PULSED WITH CTL AND/OR HTL PEPTIDES

- [00316] An embodiment of a vaccine composition in accordance with the invention comprises ex vivo administration of a cocktail of epitope-bearing peptides to PBMC, or isolated DC therefrom, from the patient's blood. A pharmaceutical to facilitate harvesting of DC can be used, such as ProgenipoietinTM (Monsanto, St. Louis, MO) or GM-CSF/IL-4. After pulsing the DC with peptides and prior to reinfusion into patients, the DC are washed to remove unbound peptides. In this embodiment, a vaccine comprises peptide-pulsed DCs which present the pulsed peptide epitopes in HLA molecules on their surfaces.
- [00317] The DC can be pulsed ex vivo with a cocktail of peptides, some of which stimulate CTL responses to one or more antigens of interest, e.g., antigens from infectious agents such as HIV env, HIV pol, HIV gag, HIV vpu, HBV and/or the antigens in Tables 11-22, or otherwise described herein or know in the art. Optionally, a helper T cell (HTL) peptide such as PADRE[®], can be included to facilitate the CTL response. Thus, a vaccine in accordance with the invention comprising epitopes from an infectious agent is used to

treat or prevent disease mediated by these agents in patients. A vaccine can be used prior to, during, or following other therapies including, for example, antibiotic therepy, anti-viral therapy (e.g., highly active antiretroviral therapy (HAART) in the case of HIV-AIDS), antibody therapy, cancer therapy, and adjunct thereapy, whereupon the vaccine provides descreased morbidity, increased disease free survival and overall survival in recipients.

DIAGNOSTIC AND PROGNOSTIC USES

- [00318] In one embodiment of the invention, HLA class I and class II binding peptides can be used as reagents to evaluate an immune response. Preferably, the following principles are utilized when selecting a variant(s) for diagnostic, prognostic and similar uses. Potential principles include having the binding affinities described earlier, and/or matching the HLA-motif/supermotif of a peptide with the HLA-type of a patient.
- [00319] The evaluated immune response can be induced by any immunogen. For example, the immunogen may result in the production of antigen-specific CTLs or HTLs that recognize the peptide epitope(s) employed as the reagent. Thus, a peptide of the invention may or may not be used as the immunogen. Assay systems that can be used for such analyses include tetramer-based protocols (e.g., DimerX technology (see, e.g., Science 274:94-99 (1996) and Proc. Natl. Acad. Sci. 95:7568-73 (1998)), staining for intracellular lymphokines, interferon release assays, or ELISPOT assays.
- [00320] For example, following exposure to a putative immunogen, a peptide of the invention can be used in a tetramer staining assay to assess peripheral blood mononuclear cells for the presence of any antigen-specific CTLs. The HLA-tetrameric complex is used to directly visualize antigen-specific CTLs and thereby determine the frequency of such antigen-specific CTLs in a sample of peripheral blood mononuclear cells (see, e.g., Ogg et al., Science 279:2103-2106, 1998; and Altman et al., Science 174:94-96, 1996).
- [00321] A tetramer reagent comprising a peptide of the invention is generated as follows:

 A peptide that binds to an HLA molecule is refolded in the presence of the corresponding HLA heavy chain and β₂-microglobulin to generate a trimolecular complex. The complex is biotinylated at the carboxyl terminal end of the HLA heavy chain, at a site that was previously engineered into the protein. Tetramer formation is then induced by adding streptavidin. When fluorescently labeled streptavidin is used, the tetrameric complex is

used to stain antigen-specific cells. The labeled cells are then readily identified, e.g., by flow cytometry. Such procedures are used for diagnostic or prognostic purposes; the cells identified by the procedure can be used for therapeutic purposes.

- responses. (see, e.g., Bertoni et al., J. Clin. Invest. 100:503-513, 1997 and Penna et al., J. Exp. Med. 174:1565-1570, 1991.) For example, a PBMC sample from an individual expressing a disease-associated antigen (e.g. an antigen from an infectious agent) can be analyzed for the presence of antigen-specific CTLs or HTLs using specific peptides. A blood sample containing mononuclear cells may be evaluated by cultivating the PBMCs and stimulating the cells with a peptide of the invention. After an appropriate cultivation period, the expanded cell population may be analyzed, for example, for CTL or for HTL activity.
- [00323] Thus, the peptides can be used to evaluate the efficacy of a vaccine. PBMCs obtained from a patient vaccinated with an immunogen may be analyzed by methods such as those described herein. The patient is HLA typed, and peptide epitopes that are bound by the HLA molecule(s) present in that patient are selected for analysis. The immunogenicity of the vaccine is indicated by the presence of CTLs and/or HTLs directed to epitopes present in the vaccine.
- [00324] The peptides of the invention may also be used to make antibodies, using techniques well known in the art (see, e.g. CURRENT PROTOCOLS IN IMMUNOLOGY, Wiley/Greene, NY; and Antibodies A Laboratory Manual Harlow, Harlow and Lane, Cold Spring Harbor Laboratory Press, 1989). Such antibodies are useful as reagents to determine the presence of disease-associated antigens. Antibodies in this category include those that recognize a peptide when bound by an HLA molecule, i.e., antibodies that bind to a peptide-MHC complex.

ADMINISTRATION FOR THERAPEUTIC OR PROPHYLACTIC PURPOSES

[00325] The peptides and polynucleotides of the present invention, including cells and compositions comprising them, are useful for administration to mammals, particularly humans, to treat and/or prevent infection by an infectious agent such as HIV, HBV, HCV, HPV, Plasmodium falciparum and other agents described herein or known in the art. Vaccine compositions containing the peptides of the invention are administered to a

patient infected with a particular infectious agent or to an individual susceptible to, or otherwise at risk for, infection with such an agent to elicit an immune response against antigens of that agent and thus enhance the patient's own immune response capabilities. Where susceptible individuals are identified prior to infection, the composition can be targeted to them, thus minimizing the need for administration to a larger population.

- [00326] In therapeutic applications, peptide and/or nucleic acid compositions are administered to a patient in an amount sufficient to elicit an effective immune response to the infectious agent antigen and to thereby cure, arrest or slow symptoms and/or complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on, e.g., the particular composition administered, the manner of administration, the stage and severity of the disease being treated, the weight and general state of health of the patient, and the judgment of the prescribing physician.
- [00327] The vaccine compositions of the invention can be used purely as prophylactic agents. Generally the dosage for an initial prophylactic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1000 μg of peptide and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg of peptide. Dosage values for a human typically range from about 500 μg to about 50,000 μg of peptide per 70 kilogram patient. This is followed by boosting dosages of between about 1.0 μg to about 50,000 μg of peptide, administered at defined intervals from about four weeks to six months after the initial administration of vaccine. The immunogenicity of the vaccine may be assessed by measuring the specific activity of CTL and HTL obtained from a sample of the patient's blood.
- [00328] As noted above, peptides comprising CTL and/or HTL epitopes of the invention induce immune responses when presented by HLA molecules and contacted with a CTL or HTL specific for an epitope comprised by the peptide. The manner in which the peptide is contacted with the CTL or HTL is not critical to the invention. For instance, the peptide can be contacted with the CTL or HTL either in vitro or in vivo. If the contacting occurs in vivo, peptide can be administered directly, or in other forms/vehicles, e.g., DNA vectors encoding one or more peptides, viral vectors encoding the peptide(s), liposomes, antigen presenting cells such as dendritic cells, and the like.
- [00329] Accordingly, for pharmaceutical compositions of the invention in the form of peptides or polypeptides, the peptides or polypeptides can be administered directly. Alternatively, the peptide/polypeptides can be administered indirectly presented on APCs, or as DNA encoding them. Furthermore, the peptides or DNA encoding them can be administered individually or as fusions of one or more peptide sequences.
- [00330] For therapeutic use, administration should generally begin at the first diagnosis of infectious agent-related disease. This is followed by boosting doses at least until symptoms are

substantially abated and for a period thereafter. In chronic disease states, loading doses followed by boosting doses may be required.

- [00331] The dosage for an initial therapeutic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1,000 μg of peptide and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg of peptide. Dosage values for a human typically range from about 500 μg to about 50,000 μg of peptide per 70 kilogram patient. Boosting dosages of between about 1.0 μg to about 50,000 μg of peptide, administered pursuant to a boosting regimen over weeks to months, can be administered depending upon the patient's response and condition. Patient response can be determined by measuring the specific activity of CTL and HTL obtained from the patient's blood.
- [00332] In certain embodiments, peptides and compositions of the present invention are used in serious disease states. In such cases, as a result of the minimal amounts of extraneous substances and the relative nontoxic nature of the peptides, it is possible and may be desirable to administer substantial excesses of these peptide compositions relative to these stated dosage amounts.
- [00333] For treatment of chronic disease, a representative dose is in the range disclosed above, namely where the lower value is about 1, 5, 50, 500, or 1,000 µg of peptide and the higher value is about 10,000; 20,000; 30,000; or 50,000 µg of peptide, preferably from about 500 µg to about 50,000 µg of peptide per 70 kilogram patient. Initial doses followed by boosting doses at established intervals, e.g., from four weeks to six months, may be required, possibly for a prolonged period of time to effectively immunize an individual. In the case of chronic disease, administration should continue until at least clinical symptoms or laboratory tests indicate that the disease has been eliminated or substantially abated, and for a follow-up period thereafter. The dosages, routes of administration, and dose schedules are adjusted in accordance with methodologies known in the art.
- [00334] The pharmaceutical compositions for therapeutic treatment are intended for parenteral, topical, oral, intrathecal, or local administration. Preferably, the pharmaceutical compositions are administered parentally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly.
- [00335] Thus, in a preferred embodiment the invention provides compositions for parenteral administration which comprise a solution of the immunogenic peptides dissolved or suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.8% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances or pharmaceutical excipients as may be required to approximate physiological conditions, such as pH-adjusting and

buffering agents, tonicity adjusting agents, wetting agents, preservatives, and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

- [00336] The concentration of peptides of the invention in the pharmaceutical formulations can vary widely, *i.e.*, from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight, and will be selected primarily by fluid volumes, viscosities, *etc.*, in accordance with the particular mode of administration selected.
- [00337] A human unit dose form of the peptide composition is typically included in a pharmaceutical composition that also comprises a human unit dose of an acceptable carrier, preferably an aqueous carrier, and is administered in a volume of fluid that is known by those of skill in the art to be used for administration of such compositions to humans (see, e.g., Remington's Pharmaceutical Sciences, 17th Edition, A. Gennaro, Editor, Mack Publishing Co., Easton, Pennsylvania, 1985).
- The peptides of the invention can also be administered via liposomes, which serve to [00338] target the peptides to a particular tissue, such as lymphoid tissue, or to target selectively to infected cells, as well as to increase the half-life of the peptide composition. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations, the peptide to be delivered is incorporated as part of a liposome, alone or in conjunction with a molecule which binds to a receptor prevalent among lymphoid cells (such as monoclonal antibodies which bind to the CD45 antigen) or with other therapeutic or immunogenic compositions. Thus, liposomes either filled or decorated with a desired peptide of the invention can be directed to the site of lymphoid cells, where the liposomes then deliver the peptide compositions. Liposomes for use in accordance with the invention are formed from standard vesicle-forming lipids, which generally include neutral and negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of, e.g., liposome size, acid lability and stability of the liposomes in the blood stream. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et . al., Ann. Rev. Biophys. Bioeng. 9:467 (1980), and U.S. Patent Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369.
- [00339] For targeting compositions of the invention to cells of the immune system, a ligand can be incorporated into the liposome, e.g., antibodies or fragments thereof specific for cell surface determinants of the desired immune system cells. A liposome suspension containing a peptide may be administered intravenously, locally, topically, etc. in a dose which varies according to, inter alia, the manner of administration, the peptide being delivered, and the stage of the disease being treated.

[00340] For solid compositions, conventional nontoxic solid carriers may be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10-95% of active ingredient, that is, one or more peptides of the invention, often at a concentration of 25%-75%.

[00341] For aerosol administration, the immunogenic peptides are preferably supplied in finely divided form, along with a surfactant and propellant. Typical percentages of peptides are 0.01%-20% by weight, often 1%-10%. The surfactant must, of course, be pharmaceutically acceptable, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant, although an atomizer may be used in which no propellant is necessary and other percentages are adjusted accordingly. A carrier can also be included, e.g., lecithin for intranasal delivery.

Antigenic peptides of the invention have been used to clicit a CTL and/or HTL response ex vivo, as well. The resulting CTLs or HTLs can be used to treat chronic infections, or tumors in patients that do not respond to other conventional forms of therapy, or who do not respond to a therapeutic peptide or nucleic acid vaccine in accordance with the invention. Ex vivo CTL or HTL responses to a particular antigen (infectious or tumor-associated) are induced by incubating in tissue culture the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of antigen-presenting cells (APC), such as dendritic cells, and the appropriate immunogenic peptide. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused back into the patient, where they will destroy (CTL) or facilitate destruction (HTL) of their specific target cell (an infected cell or a tumor cell).

KITS

[00343] The peptide and nucleic acid compositions of this invention can be provided in kit form together with instructions for vaccine administration. Typically the kit would include desired composition(s) of the invention in a container, preferably in unit dosage form and instructions for administration. For example, a kit would include an APC, such

as a dendritic cell, previously exposed to and now presenting peptides of the invention in a container, preferably in unit dosage form together with instructions for administration. An alternative kit would include a minigene construct with desired nucleic acids of the invention in a container, preferably in unit dosage form together with instructions for administration. Lymphokines such as IL-2 or IL-12 may also be included in the kit. Other kit components that may also be desirable include, for example, a sterile syringe, booster dosages, and other desired excipients.

[00344] The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters that can be changed or modified to yield alternative embodiments in accordance with the invention.

EXAMPLES

EXAMPLE 1. HLA CLASS I AND CLASS II BINDING ASSAYS

- [00345] The following example of peptide binding to HLA molecules demonstrates quantification of binding affinities of HLA class I and class II peptides. Binding assays can be performed with peptides that are either motif-bearing or not motif-bearing.
- [00346] Cell lysates were prepared and HLA molecules purified in accordance with disclosed protocols (Sidney et al., Current Protocols in Immunology 18.3.1 (1998); Sidney, et al., J. Immunol. 154:247 (1995); Sette, et al., Mol. Immunol. 31:813 (1994)). The cell lines used as sources of HLA molecules and the antibodies used for the extraction of the HLA molecules from the cell lysates are also described in these publications and are well known in the art.
- [00347] Epstein-Barr virus (EBV)-transformed homozygous cell lines, fibroblasts, CIR, or 721.221-transfectants were used as sources of HLA class I molecules. These cells were cultured in RPMI 1640 medium supplemented with 2mM L-glutamine (GIBCO, Grand Island, NY), 50μM 2-ME, 100μg/ml of streptomycin, 100U/ml of penicillin (Irvine Scientific) and 10% heat-inactivated FCS (Irvine Scientific, Santa Ana, CA).
- [00348] Cell lysates were prepared as follows. Briefly, cells were lysed at a concentration of 10⁸ cells/ml in 50 mM Tris-HCl, pH 8.5, containing 1% Nonidet P-40 (Fluka

Biochemika, Buchs, Switzerland), 150 mM NaCl, 5 mM EDTA, and 2 mM PMSF. Lysates were cleared of debris and nuclei by centrifugation at 15,000 x g for 30min.

[00349] HLA molecules were purified from lysates by affinity chromatography. Lysates were passed twice through two pre-columns of inactivated Sepharose CL4-B and protein A-Sepharose. Next, the lysate was passed over a column of Sepharose CL-4B beads coupled to an appropriate antibody. The anti-HLA column was then washed with 10-column volumes of 10mM Tris-HCL, pH 8.0, in 1% NP-40, PBS, 2-column volumes of PBS, and 2-column volumes of PBS containing 0.4% n-octylglucoside. Finally, MHC molecules were cluted with 50mM diethylamine in 0.15M NaCl containing 0.4% n-octylglucoside, pH 11.5. A 1/25 volume of 2.0M Tris, pH 6.8, was added to the cluate to reduce the pH to ~8.0. Eluates were then concentrated by centrifugation in Centriprep 30 concentrators at 2000 rpm (Amicon, Beverly, MA). Protein content was evaluated by a BCA protein assay (Pierce Chemical Co., Rockford, IL) and confirmed by SDS-PAGE.

[00350] A detailed description of the protocol utilized to measure the binding of peptides to Class I and Class II MHC has been published (Sette et al., Mol. Immunol. 31:813, 1994; Sidney et al., in Current Protocols in Immunology, Margulies, Ed., John Wiley & Sons, New York, Section 18.3, 1998). Briefly, purified MHC molecules (5 to 500nM) were incubated with various unlabeled peptide inhibitors and 1-10nM ¹²⁵I-radiolabeled probe peptides for 48h in PBS containing 0.05% Nonidet P-40 (NP40) (or 20% w/v digitonin for H-2 IA assays) in the presence of a protease inhibitor cocktail. The final concentrations of protease inhibitors (each from CalBioChem, La Jolla, CA) were 1 mM PMSF, 1.3 nM 1.10 phenanthroline, 73 μM pepstatin A, 8mM EDTA, 6mM N-ethylmaleimide (for Class II assays), and 200 μM N alpha-p-tosyl-L-lysine chloromethyl ketone (TLCK). All assays were performed at pH 7.0 with the exception of DRB1*0301, which was performed at pH 4.5, and DRB1*1601 (DR2w21β1) and DRB4*0101 (DRw53), which were performed at pH 5.0. pH was adjusted as described elsewhere (see Sidney et al., in Current Protocols in Immunology, Margulies, Ed., John Wiley & Sons, New York, Section 18.3, 1998).

[00351] Following incubation, MHC-peptide complexes were separated from free peptide by gel filtration on 7.8 mm x 15 cm TSK200 columns (TosoHaas 16215, Montgomeryville, PA), eluted at 1.2 mls/min with PBS pH 6.5 containing 0.5% NP40 and 0.1% NaN₃. Because the large size of the radiolabeled peptide used for the DRB1*1501 (DR2w2β₁) assay makes separation of bound from unbound peaks more difficult under these conditions, all DRB1*1501 (DR2w2β₁) assays were performed using a 7.8mm x

30cm TSK2000 column eluted at 0.6 mls/min. The eluate from the TSK columns was passed through a Beckman 170 radioisotope detector, and radioactivity was plotted and integrated using a Hewlett-Packard 3396A integrator, and the fraction of peptide bound was determined.

[00352] Radiolabeled peptides were iodinated using the chloramine-T method. Representative radiolabeled probe peptides utilized in each assay, and its assay specific IC₅₀ nM, are known in the art. Typically, in preliminary experiments, each MHC preparation was titered in the presence of fixed amounts of radiolabeled peptides to determine the concentration of HLA molecules necessary to bind 10-20% of the total radioactivity. All subsequent inhibition and direct binding assays were performed using these HLA concentrations.

[00353] Since under these conditions [label]<[HLA] and IC₅₀≥[HLA], the measured IC₅₀ values are reasonable approximations of the true K_D values. Peptide inhibitors are typically tested at concentrations ranging from 120 μg/ml to 1.2 ng/ml, and are tested in two to four completely independent experiments. To allow comparison of the data obtained in different experiments, a relative binding figure is calculated for each peptide by dividing the IC₅₀ of a positive control for inhibition by the IC₅₀ for each tested peptide (typically unlabeled versions of the radiolabeled probe peptide). For inter-experiment comparisons, relative binding values are compiled. These values can subsequently be converted back into IC₅₀ nM values by dividing the IC₅₀ nM of the positive controls for inhibition by the relative binding of the peptide of interest. This method of data compilation has proven to be the most accurate and consistent for comparing peptides that have been tested on different days, or with different lots of purified MHC.

[00354] Because the antibody used for HLA-DR purification (LB3.1) is α-chain specific, β₁ molecules are not separated from β₃ (and/or β₄ and β₅) molecules. The β₁ specificity of the binding assay is obvious in the cases of DRB1*0101 (DR1), DRB1*0802 (DR8w2), and DRB1*0803 (DR8w3), where no β₃ is expressed. It has also been demonstrated for DRB1*0301 (DR3) and DRB3*0101 (DR52a), DRB1*0401 (DR4w4), DRB1*0404 (DR4w14), DRB1*0405 (DR4w15), DRB1*1101 (DR5), DRB1*1201 (DR5w12), DRB1*1302 (DR6w19) and DRB1*0701 (DR7). The problem of β chain specificity for DRB1*1501 (DR2w2β₁), DRB5*0101 (DR2w2β₂), DRB1*1601 (DR2w21β₁), DRB5*0201 (DR51Dw21), and DRB4*0101 (DRw53) assays is circumvented by the use

of fibroblasts. Development and validation of assays with regard to DRβ molecule specificity have been described previously (see, e.g., Southwood et al., J. Immunol. 160:3363-3373, 1998).

[00355] Binding assays as outlined above may be used to analyze supermotif and/or motifbearing epitopes.

EXAMPLE 2. RECOGNITION OF VARIANT PEPTIDES BY CTL DERIVED FROM DNA IMMUNIZATION

Variants corresponding to five HLA-A2 and -A3 restricted epitopes from 167 HIV varianst were identified and synthesized. These represented all the complete sequences in the Los Alamos database at the time (116 strains), as well as 51 complete clade C sequences from Botswana, and included 22 subtype B and 62 subtype C sequences. These peptides were then characterized with regard to MHC binding, variant distribution, and immunogenicity. To measure immunogenicity, HLA-A2/K^b or HLA-A11/K^b transgenic mice were immunized with the epitopes encoded in a DNA based format (). Eleven days after immunization, splenocytes were restimulated with either the epitope corresponding to the epitope encoded by the DNA (parent) or each of the variant peptides. After 6 days in culture, IFN-γ secretion was measured in response to the peptide used to stimulate each culture.

The data for these epitopes are shown in Figure 1. The HLA-A2-restricted epitope corresponding to the Env 134 epitope (KLTPLCVTL; Figure 1A) used as the immunogen was the form observed most often (134/167). All single anchor variants were recognized to approximately the same extent as the parent peptide. Many of the single non-anchor variants (9/13) were also recognized within 10-fold of the parent peptide. Conservative substitutions (R and Q for K; see Table 4) at position 1 (P1) were tolerated, while the non-conservative substitution (E for K; see Table 4) lowered binding and eliminated recognition. Three P4 variants were observed. Two of these (F or S for P) were recognized within 10-fold of the recognition of the parent peptide, while one substitution (Q for P) completely eliminated recognition. The binding for these peptides was not significantly different from the parent peptide, indicating that this residue may be involved in TCR recognition. Both the conservative (F for L) and non-conservative (R for L) substitutions

seen at P5 completely abrogated recognition, indicating that this residue is important in TCR recognition. Finally, one substitution at P8 (I for V), and four substitutions at P9 show little effect on recognition. None of the variants with multiple substitutions were recognized, although this may be due to the poor binding of these peptides.

[00358] The Gag 386 sequence utilized as the immunogen was the second most common form (VLAEAMSQV), present in 54 strains (Figure 1B). The most prevalent variant, differing by a single tolerated C terminal anchor residue (V to A; 67 strains), was recognized equally to the parent epitope by CTL raised against the parent, as were the remaining single-anchor variants. Single substitutions were also tolerated at the non-anchor positions, P1 (I for V) and P8 (R, K, or H for Q). Only the P7 variant (G for S), probably a TCR contact residue, was not recognized.

[00359] Many of the multiple variants for Gag 386 were also recognized by CTL raised against the parent peptide. All the variants with multiple changes combined a change of V to A or T at the C terminus with 1-3 additional substitutions. Two variants with N terminal changes (V to A or I) were observed. The non-conservative A substitution was not recognized, while the conservative I substitution was. A double variant with a conservative substitution at P3 (A to G) was not recognized, implicating P3 in TCR recognition. Double variants with conservative changes at position 8 (Q to R, K, or H) were not well recognized, although the variants with single changes at the same positions were recognized. The variant combining a non-conservative A residue at position 8 with A at the C terminus was recognized as well as the parent. Equally surprising was the observation that all the variants with 3 or 4 substitutions were recognized within 10-fold of the parent peptide.

The parent form of the HLA-A2-restricted epitope, Vpr 62 (RILQQLLFI; Figure 1C) was the most common form observed (86/167). Seven well-tolerated single anchor substitutions, 4 P2 and 3 C terminal, were also observed, accounting for most of the remaining variants (47/167). Single substitutions were, in general, also well tolerated. The single exception was the non-conservative substitution (P for L) at P6, while an M for L substitution at the same site was well tolerated. Binding was not affected for either variant, indicating that the reduction in activity is due to a change in a contact residue. Most variants with multiple changes also showed recognition to approximately the same extent as the parent. Several variants however did show reduced recognition. The variant with changes at both anchors (I to T at P2 and I to T at P9) had reduced binding (IC₅₀ of 9700),

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and recognition of the peptide was reduced, although not lost completely. Two variants with Q to H changes at P5, in combination with anchor residue changes (I to M at P2 and I to A at P9), exhibited greatly reduced recognition although binding was not affected. Other changes at P5 (Q to R or L at P5) reduced recognition only slightly.

- [00361] The HLA-A3/11-restricted epitope, Pol 98 (Figure 1D), represented the most diverse epitope in terms of the number of variant epitopes identified. The peptide encoded in the DNA was represented in only 18 out of 167 strains. Approximately a third of the peptides identified at that position (49 out of 167) did not have recognizable A3/A11 motifs. The most common variant (30 strains) differed from the parent peptide at 3 residues (VSIKVGGQIK), but was recognized within 10-fold of the parent peptide. Two variants with conservative changes at anchor residues were both recognized, although the T to A substitution at P2 resulted in a 10-fold reduction in recognition of the variant peptide. All peptides with single changes in non-anchor positions were also recognized, although the P5 variant (G to E) exhibited a decrease in recognition. As the binding was not affected, this probably indicates involvement in T cell recognition.
- [00362] Peptides with two changes showed mixed results. In general, peptides with a V substitution at position 3, in combination with another substitution were recognized to the same extent as the corresponding single substitution, indicating the V substitution was tolerated well and is not a TCR contact residue. Combinations including the P2 anchor residue (T to A or N) were not recognized, although the binding of these peptides was also low. Variants with 3 substitutions were generally not recognized well. Two exceptions with very conservative substitutions were noted (Figure 1D). CTL were unable to recognize peptides with four or more substitutions.
- [00363] The HLA-A3/11- restricted Env 47 epitope (Figure 1E; VTVYYGVPVWK) was highly conserved, with only 9 variants identified. The most common form observed was the parent peptide (99 strains), while the second most common form, a single anchor substitution observed in 40 strains, was recognized to the same extent as the parent. All the variants were recognized within 10-fold of the parent epitope.
- [00364] Taken together, these data show trends towards promiscuous recognition of variant peptides by CTL generated from immunization with a single peptide. In general, changes that disrupted binding also decreased recognition. Recognition was also affected by the position of the change, with potential TCR contact residues (P3-7) exerting a greater effect on recognition than other residues. In general, conservative residue changes were more

widely tolerated than were non-conservative changes. Recognition was also dependent on the number of changes, with progressively lower recognition with a greater number of changes.

[00365] Recognition after multiple restimulations The observed recognition of variant peptides by CTL raised against the parent peptide might be due to either promiscuous recognition at the level of a single TCR or simply a mixture of TCRs against the immunizing peptide which are each able to recognize subtly different peptides. To distinguish between these two possibilities, Env 134- or Gag 386-specific T cell lines were generated by stimulating five times with the immunizing peptide, and then tested for recognition of a partial panel of variant peptides. These T cell lines were also characterized for Vβ TCR usage against a panel of antibodies predicted to react with the TCR of the mouse strains utilized for these experiments.

[00366] The data for these peptide-specific lines are shown in Table 5. Because the SU is a measure of the number of cells needed to secrete a defined amount of IFN-γ, a higher SU value would correspond to an enrichment of IFN-γ producing cells. A comparison of one and five peptide stimulations indeed shows an enrichment of CTL specific for the immunizing peptide for both of the peptide lines generated (Table 5A and 5B, first line). The Gag 386 line (Table 5A) also demonstrated increased recognition of all the variant peptides measured except one peptide (ILAEAMSKA) that was never recognized. The Env 134 line also demonstrated enrichment for CTL able to recognize several of the variant peptides (Table 5B).

[00367] To further characterize these lines, we examined them for Vβ usage, utilizing a panel of commercially available antibodies available for mouse TCR Vβ 2-14. To determine background levels for the various TCR Vβ molecules, primary splenocytes from mice that had been immunized with EP HIV-1090 were also examined. The results for the Gag 386 line are shown in Figure 2A. After a single stimulation with the parent peptide, the Gag 386 line showed a mixture of TCR positive populations, including Vβ 3, 5, and 14. After 5 stimulations, those populations had been reduced to background levels, and approximately 50% of the CD8+ cells expressed the Vβ 6 TCR. The Env 134 line showed a similar pattern of multiple TCR positive populations after a single round of stimulation with reduction to background levels after 5 stimulations (data not shown). However, no

single $V\beta$ usage significantly above background could be demonstrated, probably due to lack of the relevant TCR $V\beta$ antibody.

- [00368] Both lines were also characterized with regard to the affinity of certain of the variant peptides by titrating the variant peptides examined above (Table 5A and 5B). The data for both the Gag 386 and Env 134 lines are shown in Figure 2B. For the Gag 386 line, the parent peptide along with two single anchor variants (VLAEAMSQI and VLAEAMSQA) showed the highest affinity. Four other peptides demonstrated lower affinity, but still produced IFN-γ in response to higher peptide concentrations. A single peptide (ILAEAMSKA) was not recognized.
- [00369] As expected, the parent peptide, which was used to generate the Env 134 line, showed the highest affinity for the TCR. The other 2 variant peptides, KITPLCVTL and QLTPLCVTL, also demonstrated higher affinity, but reduced from the parent peptide by approximately 10-fold and 100-fold, respectively. It was notable that only at the highest peptide concentration examined (1 μg/ml) was any IFN-γ secretion detected for five of the peptides (QITPLCVTL, ELTPLCVTL, KLTPFCVTL, KLTPLCVIL, and KLTPLCVPL). These five peptides showed little or no enrichment of CTL able to recognize them, and exhibited the lowest activity as measured by SU after five restimulations (see Table 5B).
- [00370] In summary, these cell lines seem to consist of a narrow, possibly single, TCR population. This TCR population recognizes the parent peptide with the highest affinity, but is also able to recognize a number of other variant peptides with equal or lesser affinity.

[00371] Recognition of variant peptides by CTL derived from an HIV infected patient.

[00372] To determine if the same immunological conservation was observed in natural infections, we identified an HIV-infected individual expressing the HLA-A3 allele. The HIV strain and subtype with which this patient was infected is unknown. We had previously shown that T cells from this individual responded to the HLA-A3 restricted epitopes Pol 98 and Env 47. PBL from this patient were examined in an ELISPOT assay to determine if they also showed the capacity for broad cross-reactivity. The data are shown in Figure 3. Although the actual peptide represented in the HIV strain with which this individual is infected is unknown, we observed recognition of a large number of the variant peptides for both Pol 98 (Figure 3A) and Env 47 (Figure 3B). The recognition patterns were remarkably similar for the mouse and patient data (compare Figure 1 and

Figure 3), although the mouse expressed a transgene for HLA-A11 and the patient was HLA-A3.

[00373] Prediction of Immunological Conservation. We had observed that the variant peptides that were recognized by CTL raised against the parent epitope had amino acid substitutions that followed previous observations. For example, the anchor residue changes that were tolerated in the variant peptides were also described as anchors that to define the respective HLA supertypes (). In general, conservative substitutions were tolerated at non-anchor residues, while non-conservative substitutions were less well tolerated. These followed closely the prediction model used to identify heteroclitic analogs (Tangri et al).

[00374] Based on these observations, we designed a computer program to predict immunological conservation. For anchor positions, this program utilized the conserved anchor residues described for the A2, A3, and B7 supertypes. For non-anchor positions only conservative substitutions, as defined in Tangri et.al. (), were allowed. All substitutions at non-anchor positions were analyzed independently and all conservative substitutions were allowed regardless of the number of substitutions. Finally, the position of the substitution was not factored into analysis. Each variant was compared with the parent epitope, and its ability to be recognized was predicted as either positive or negative.

[00375] The first sets of epitopes to be evaluated by this program were the five HIV epitopes and variants previously described. For the Env 134 epitope, the program predicted that 13 of the variant peptides should be immunologically conserved, while 6 should not be recognized. Comparison of the observed immunological data with the prediction showed that the program predicted correctly for 14 of the peptides and incorrectly for 5. Of the incorrect predictions, in two cases the program predicted negative results for peptides that were recognized, while in 3 cases the program predicted positive results for peptides that were not recognized. A similar analysis was performed for all five peptides. Of 101 total variant peptides, 68 were correctly identified (67%). The discordant data were fairly evenly split between peptides incorrectly predicted negative (15) and those incorrectly predicted positive (18).

[00376] As noted previously, the more substitutions present in a variant peptide, the lower the likelihood of its immunogenicity. Since the prediction program treated all substitutions independently, and did not take into account the number of substitutions, we hypothesized

that prediction of single substitutions would be more accurate. Indeed, the immunogenicity of 38 of 47 single substitution variants (80%) was correctly predicted.

[00377] With the limitations of the program in mind, it is useful to predict the recognition of the variants for a package of HLA-A2, -A3, and -B7 supertype epitopes. These epitopes had been identified as being well conserved in Clade B variants. When comparing the conservation of this group of epitopes based on sequence identity versus immunological conservation, it is interesting to note that the predicted recognition gains taking into account immunological conservation are significant (Table 6).

This particular group of 21 epitopes was selected based on their identity [00378] conservation in Clade B HIV sequences, with conservation across HIV clades as a secondary consideration. Because of this criteria, the form of epitope chosen as the parent peptide was not the most common variant (e.g. Gag 386, Gag 271, Pol 98). In some cases (e.g., see Gag 386 data), the "parent" epitope and the most common variant were recognized to the same extent. However, in some cases the selection of epitope to include as the "parent" epitope was predicted to make a difference in the immunological conservation. An example of this was the Gag 271 epitope (Figure 4). The variant most commonly seen in clade B sequences was the MTNNPPIPV form, while the most common form of the epitope was MTSNPPIPV. Not all amino acids are considered equal to each other in their ability to substitute (Tangri). For example, asparagine (N) is considered a conservative substitution for serine (S), while the opposite substitution in only considered semi-conserved. When the program calculated immunological conservation using the MTNNPPIPV peptide as the parent peptide, only two variants were predicted to be immunogenic. However, when the immunological conservation was predicted using the MTSNPPIPV peptide, most of the variants were predicted to be recognized (Figure 4). This prediction was tested using HLA-A2 transgenic mice. The results show that if the MTSNPPIPV form of the peptide was utilized in vaccines, approximately 152 of 167 variants would be recognized, while if the MTNNPPIPV form of the epitope was utilized, only 39 of 167 variants would be recognized. This has important implications in epitope selection for vaccine development, and epitope performance can be predicted.

EXAMPLE 3. A PADRE® MOLECULE AS A HELPER EPITOPE FOR ENHANCEMENT OF CTL INDUCTION

- Interest is increasing evidence that HTL activity is critical for the induction of long lasting CTL responses (Livingston et al. J. Immunol 162:3088-3095 (1999); Walter et al., New Engl. J. Med. 333:1038-1044 (1995); Hu et al., J. Exp. Med. 177:1681-1690 (1993)). Therefore, one or more peptides that bind to HLA class II molecules and stimulate HTLs can be used in accordance with the invention. Accordingly, a preferred embodiment of a vaccine includes a molecule from the PADRE® family of universal T helper cell epitopes (HTL) that target most DR molecules in a manner designed to stimulate helper T cells. For instance, a pan-DR-binding epitope peptide having the formula: aKXVAAZTLKAAa, where "X" is either cyclohexylalanine, phenylalanine, or tyrosine; "Z" is either tryptophan, tyrosine, histidine or asparagine; and "a" is either D-alanine or L-alanine (SEQ ID NO:29), has been found to bind to most HLA-DR alleles, and to stimulate the response of T helper lymphocytes from most individuals, regardless of their HLA type.
- [00380] A particularly preferred PADRE® molecule is a synthetic peptide, aKXVAAWTLKAAa (a = D-alanine, X = cyclohexylalanine), containing non-natural amino acids, specifically engineered to maximize both HLA-DR binding capacity and induction of T cell immune responses.
- [00381] Alternative preferred PADRE® molecules are the peptides, aKFVAAWTLKAAa, aKYVAAWTLKAAa, aKYVAAYTLKAAa, aKXVAAYTLKAAa, aKYVAAYTLKAAa, aKYVAAHTLKAAa, aKYVAAHTLKAAa, aKFVAANTLKAAa, aKYVAAHTLKAAa, aKYVAANTLKAAa, aKYVAANTLKAAA, aKXVAAWTLKAAA (SEQ ID NO:30), AKFVAAWTLKAAA (SEQ ID NO:31), AKYVAAWTLKAAA (SEQ ID NO:32), AKFVAAYTLKAAA (SEQ ID NO:33), AKXVAAYTLKAAA (SEQ ID NO:34), AKYVAAYTLKAAA (SEQ ID NO:35), AKFVAAHTLKAAA (SEQ ID NO:36), AKXVAAHTLKAAA (SEQ ID NO:37), AKYVAAHTLKAAA (SEQ ID NO:38), AKFVAANTLKAAA (SEQ ID NO:39), AKXVAANTLKAAA (SEQ ID NO:40), AKYVAANTLKAAA (SEQ ID NO:41) (a = D-alanine, X = cyclohexylalanine).
- [00382] In a preferred embodiment, the PADRE® peptide is amidated. For example, a particularly preferred amidated embodiment of a PADRE® molecule is conventionally written aKXVAAWTLKAAa-NH₂.

[00383] Competitive inhibition assays with purified HLA-DR molecules demonstrated that the PADRE® molecule aKXVAAWTLKAAa-NH₂ binds with high or intermediate affinity (IC₅₀ ≤1,000 nM) to 15 out of 16 of the most prevalent HLA-DR molecules ((Kawashima et al., Human Immunology 59:1-14 (1998); Alexander et al., Immunity 1:751-761 (1994)). A comparison of the DR binding capacity of PADRE® and tetanus toxoid (TT) peptide 830-843, a "universal" epitope has been published (Panina-Bordignon et al., Eur. J. Immunology 19:2237-2242 (1989)). The TT 830-843 peptide bound to only seven of 16 DR molecules tested, while PADRE® bound 15 of 16. At least 1 of the 15 DR molecules that bind PADRE® is predicted to be present in >95% of all humans. Therefore, this PADRE® molecule is anticipated to induce an HTL response in virtually all patients, despite the extensive polymorphism of HLA-DR molecules in the human population.

[00384] PADRE® has been specifically engineered for optimal immunogenicity for human T cells. Representative data from *in vitro* primary immunizations of normal human T cells with TT 830-843 antigen and the PADRE® molecule aKXVAAWTLKAAa-NH₂ are shown in Figure 1. Peripheral blood mononuclear cells (PBMC) from three normal donors were stimulated with the peptides *in vitro*. Following the third round of stimulation, it was observed that PADRE® generated significant primary T cell responses for all three donors as measured in a standard T cell proliferation assay. With the PADRE® peptide, the 10,000 cpm proliferation level was generally reached with 10 to 100 ng/ml of antigen. In contrast, TT 830-843 antigen generated responses for only 2 out of 3 of the individuals tested. Responses approaching the 10,000 cpm range were reached with about 10,000 ng/ml of antigen. In this respect, it was noted that PADRE® was, on a molar basis, about 100-fold more potent than TT 830-843 antigen for activation of T cell responses.

[00385] Early data from a phase I/II investigator-sponsored trial, conducted at the University of Leiden (C.J.M. Melief), support the principle that the PADRE® molecule aKXVAAWTLKAAa, possibly the amidated aKXVAAWTLKAAa -NH₂, is highly immunogenic in humans (Ressing et al., J. Immunother. 23(2):255-66 (2000)). In this trial, a PADRE® molecule was co-emulsified with various human papilloma virus (HPV)-derived CTL epitopes and was injected into patients with recurrent or residual cervical carcinoma. However, because of the late stage of carcinoma with the study patients, it was expected that these patients were immunocompromised. The patients' immunocompromised status was demonstrated by their low frequency of influenza virus-

specific CTL, reduced levels of CD3 expression, and low incidence of proliferative recall responses after *in vitro* stimulation with conventional antigens. Thus, no efficacy was anticipated in the University of Leiden trial, rather the goal of that trial was essentially to evaluate safety. Safety was, in fact, demonstrated. In addition to a favorable safety profile, PADRE® T cell reactivity was detected in four of 12 patients (Figure 2) in spite of the reduced immune competence of these patients.

[00386] Thus, the PADRE® peptide component(s) of the vaccine bind with broad specificity to multiple allelic forms of HLA-DR molecules. Moreover, PADRE® peptide component(s) bind with high affinity (IC₅₀ ≤1000 nM), i.e., at a level of affinity correlated with being immunogenic for HLA Class II restricted T cells. The *in vivo* administration of PADRE® peptide(s) stimulates the proliferation of HTL in normal humans as well as patient populations.

[00387] One or more PADRE® peptide(s) may be included in a composition, e.g., a vaccine, comprising one or more peptides, either as an individual peptide(s), fused to one or more variant peptides, or both.

EXAMPLE 4. CTL RECOGNITION OF ENDOGENOUS PROCESSED ANTIGENS AFTER PRIMING

[00388] This example determines that CTL induced by native or analoged peptide epitopes recognize endogenously synthesized, *i.e.*, native antigens.

[00389] Effector cells isolated from transgenic mice that are immunized with peptide epitopes are re-stimulated *in vitro* using peptide-coated stimulator cells. Six days later, effector cells are assayed for cytotoxicity and the cell lines that contain peptide-specific cytotoxic activity are further re-stimulated. An additional six days later, these cell lines are tested for cytotoxic activity on ⁵¹Cr labeled Jurkat-A2.1/K^b target cells in the absence or presence of peptide, and also tested on ⁵¹Cr labeled target cells bearing the endogenously synthesized antigen, *i.e.* cells that are stably transfected with HIV expression vectors.

[00390] The result will demonstrate that CTL lines obtained from animals primed with peptide epitope recognize endogenously synthesized HIV antigen. The choice of transgenic mouse model to be used for such an analysis depends upon the epitope(s) that is being evaluated. In addition to HLA-A*0201/K^b transgenic mice, several other transgenic

mouse models including mice with human A11, which may also be used to evaluate A3 epitopes, and B7 alleles have been characterized and others (e.g., transgenic mice for HLA-A1 and A24) are being developed. HLA-DR1 and HLA-DR3 mouse models have also been developed, which may be used to evaluate HTL epitopes.

EXAMPLE 5. ACTIVITY OF CTL-HTL CONJUGATED EPITOPES IN TRANSGENIC MICE

- of a HIV CTL/HTL peptide conjugate whereby the vaccine composition comprises peptides administered to an HIV-infected patient or an individual at risk for HIV. The peptide composition can comprise multiple CTL and/or HTL epitopes. This analysis demonstrates enhanced immunogenicity that can be achieved by inclusion of one or more HTL epitopes in a vaccine composition. Such a peptide composition can comprise an HTL epitope conjugated to a preferred CTL epitope containing, for example, at least one CTL epitope, or an analog of that epitope. The peptides may be lipidated, if desired.
- [00392] Immunization procedures: Immunization of transgenic mice is performed as described (Alexander et al., J. Immunol. 159:4753-4761, 1997). For example, A2/Kb mice, which are transgenic for the human HLA A2.1 allele and are useful for the assessment of the immunogenicity of HLA-A*0201 motif- or IILA-A2 supermotif-bearing epitopes, are primed subcutaneously (base of the tail) with a 0.1 ml of peptide in Incomplete Freund's Adjuvant, or if the peptide composition is a lipidated CTL/HTL conjugate, in DMSO/saline or if the peptide composition is a polypeptide, in PBS or Incomplete Freund's Adjuvant. Seven days after priming, splenocytes obtained from these animals are restimulated with syngenic irradiated LPS-activated lymphoblasts coated with peptide.
- [00393] Cell lines: Target cells for peptide-specific cytotoxicity assays are Jurkat cells transfected with the HLA-A2.1/K^b chimeric gene (e.g., Vitiello et al., J. Exp. Med. 173:1007, 1991).
- [00394] In vitro CTL activation: One week after priming, spleen cells (30x10⁶ cells/flask) are co-cultured at 37°C with syngeneic, irradiated (3000 rads), peptide coated

lymphoblasts (10x10⁶ cells/flask) in 10 ml of culture medium/T25 flask. After six days, effector cells are harvested and assayed for cytotoxic activity.

Assay for cytotoxic activity: Target cells (1.0 to 1.5x106) are incubated at 37°C in [00395] the presence of 200 µl of 51Cr. After 60 minutes, cells are washed three times and resuspended in R10 medium. Peptide is added where required at a concentration of 1 μg/ml. For the assay, 10^{4 51}Cr-labeled target cells are added to different concentrations of effector cells (final volume of 200 µl) in U-bottom 96-well plates. After a 6 hour incubation period at 37°C, a 0.1 ml aliquot of supernatant is removed from each well and radioactivity is determined in a Micromedic automatic gamma counter. The percent specific lysis is determined by the formula: percent specific release = 100 x (experimental release - spontaneous release)/(maximum release - spontaneous release). To facilitate comparison between separate CTL assays run under the same conditions, % 51Cr release data is expressed as lytic units/106 cells. One lytic unit is arbitrarily defined as the number of effector cells required to achieve 30% lysis of 10,000 target cells in a 6 hour 51Cr release assay. To obtain specific lytic units/106, the lytic units/106 obtained in the absence of peptide is subtracted from the lytic units/106 obtained in the presence of peptide. For example, if 30% ⁵¹Cr release is obtained at the effector (E): target (T) ratio of 50:1 (i.e., 5x10⁵ effector cells for 10,000 targets) in the absence of peptide and 5:1 (i.e., 5x10⁴ effector cells for 10,000 targets) in the presence of peptide, the specific lytic units would be: $[(1/50,000)-(1/500,000)] \times 10^6 = 18 \text{ LU}.$

[00396] The results are analyzed to assess the magnitude of the CTL responses of animals injected with the immunogenic CTL/HTL conjugate vaccine preparation and are compared to the magnitude of the CTL response achieved using the CTL epitope as outlined in above. Analyses similar to this may be performed to evaluate the immunogenicity of peptide conjugates containing multiple CTL epitopes and/or multiple HTL epitopes. In accordance with these procedures it is found that a CTL response is induced, and concomitantly that an HTL response is induced upon administration of such compositions.

EXAMPLE 6. SELECTION OF CTL AND HTL EPITOPES FOR INCLUSION IN AN HIV-SPECIFIC VACCINE.

- [00397] This example illustrates the procedure for the selection of peptide epitopes for vaccine compositions of the invention. The peptides in the composition can be in the form of a nucleic acid sequence, either single or one or more sequences (i.e., minigene) that encodes peptide(s), or can be single and/or polyepitopic peptides.
- [00398] The following principles are utilized when selecting an array of epitopes for inclusion in a vaccine composition. Each of the following principles is balanced in order to make the selection.
- [00399] Epitopes are selected which, upon administration, mimic immune responses that correlate with virus clearance. For example, if it has been observed that patients who clear HIV generate an immune response to at least 3 epitopes on at least one HIV antigen, then 3-4 epitopes should be included for HLA class I. A similar rationale is used to determine HLA class II epitopes.
- [00400] When selecting an array of HIV epitopes, it is preferred that at least some of the epitopes are derived from early and late proteins. The early proteins of HIV are expressed when the virus is replicating, either following acute or dormant infection. Therefore, it is particularly preferred to use epitopes from early stage proteins to alleviate disease manifestations at the earliest stage possible.
- [00401] Epitopes are often selected that have a binding affinity of an IC₅₀ of 500 nM or less for an HLA class I molecule, or for class II, an IC₅₀ of 1000 nM or less.
- [00402] Sufficient supermotif bearing peptides, or a sufficient array of allele-specific motif bearing peptides, are selected to give broad population coverage. For example, epitopes are selected to provide at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art, can be employed to assess breadth, or redundancy, of population coverage.
- [00403] When creating a polyepitopic compositions, e.g. a minigene, it is typically desirable to generate the smallest peptide possible that encompasses the epitopes of interest. The principles employed are similar, if not the same, as those employed when selecting a peptide comprising nested epitopes.
- [00404] In cases where the sequences of multiple variants of the same target protein are available, potential peptide epitopes can also be selected on the basis of their conservancy.

For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen.

[00405] Peptide epitopes for inclusion in vaccine compositions are, for example, selected from those listed in Tables 6-9 or Figures 1A-4. A vaccine composition comprised of selected peptides, when administered, is safe, efficacious, and elicits an immune response similar in magnitude of an immune response that clears an acute HIV infection.

EXAMPLE 7. CONSTRUCTION OF MINIGENE MULTI-EPITOPE DNA PLASMIDS

[00406] This example provides general guidance for the construction of a minigene expression plasmid. Minigene plasmids may, of course, contain various configurations of CTL and/or HTL epitopes or epitope analogs as described herein. Expression plasmids have been constructed and evaluated as described, for example, in co-pending U.S.S.N. 09/311,784 filed 5/13/99 and in Ishioka et al., J. Immunol. 162:3915-3925, 1999. An example of such a plasmid for the expression of HIV epitopes is shown in Figure 2, which illustrates the orientation of HIV peptide epitopes in a minigene construct.

[00407] A minigene expression plasmid typically includes multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes (Figure 2). Preferred epitopes are identified, for example, in Tables 6-9 and Figures 1A-4. IILA class I supermotif or motif-bearing peptide epitopes derived from multiple HIV antigens, are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. Similarly, HLA class II epitopes are selected from multiple HIV antigens to provide broad population coverage, i.e. both HLA DR-1-4-7 supermotif-bearing epitopes and HLA DR-3 motif-bearing epitopes are selected for inclusion in the minigene construct. The selected CTL and HTL epitopes are then incorporated into a minigene for expression in an expression vector.

[00408] Such a construct may additionally include sequences that direct the HTL epitopes to the endoplasmic reticulum. For example, the Ii protein may be fused to one or more HTL epitopes as described in co-pending application U.S.S.N. 09/311,784 filed 5/13/99,

wherein the CLIP sequence of the Ii protein is removed and replaced with an HLA class II epitope sequence os that HLA class II epitope is directed to the endoplasmic reticulum, where the epitope binds to an HLA class II molecules.

- [00409] This example illustrates the methods to be used for construction of a minigenebearing expression plasmid. Other expression vectors that may be used for minigene compositions are available and known to those of skill in the art.
- [00410] The minigene DNA plasmid contains a consensus Kozak sequence and a consensus murine kappa Ig-light chain signal sequence followed by CTL and/or HTL epitopes selected in accordance with principles disclosed herein. The construct can also include, for example, The sequence encodes an open reading frame fused to the Myc and His antibody epitope tag coded for by the pcDNA 3.1 Myc-His vector.
- Overlapping oligonucleotides, for example eight oligonucleotides, averaging approximately 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides, Kozak sequence, and signal sequence. The final multiepitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR. A Perkin/Elmer 9600 PCR machine is used and a total of 30 cycles are performed using the following conditions: 95°C for 15 sec, annealing temperature (5° below the lowest calculated Tm of each primer pair) for 30 sec, and 72°C for 1 min.
- [00412] For the first PCR reaction, 5 μg of each of two oligonucleotides are annealed and extended: Oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined in 100 μl reactions containing Pfu polymerase buffer (1x= 10 mM KCL, 10 mM (NH₄)₂SO₄, 20 mM Trischloride, pH 8.75, 2 mM MgSO₄, 0.1% Triton X-100, 100 μg/ml BSA), 0.25 mM each dNTP, and 2.5 U of Pfu polymerase. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product for 25 additional cycles. The full-length product is gel-purified and cloned into pCR-blunt (Invitrogen) and individual clones are screened by sequencing.

EXAMPLE 8. THE PLASMID CONSTRUCT AND THE DEGREE TO WHICH IT INDUCES IMMUNOGENICITY.

- [00413] The degree to which a plasmid construct, for example a plasmid constructed in accordance as above is able to induce immunogenicity can be evaluated *in vitro* by testing for epitope presentation by APC following transduction or transfection of the APC with an epitope-expressing nucleic acid construct. Such a study determines "antigenicity" and allows the use of human APC. The assay determines the ability of the epitope to be presented by the APC in a context that is recognized by a T cell by quantifying the density of epitope-HLA class I complexes on the cell surface. Quantitation can be performed by directly measuring the amount of peptide eluted from the APC (see, e.g., Sijts et al., J. Immunol. 156:683-692, 1996; Demotz et al., Nature 342:682-684, 1989); or the number of peptide-HLA class I complexes can be estimated by measuring the amount of lysis or lymphokine release induced by infected or transfected target cells, and then determining the concentration of peptide necessary to obtained equivalent levels of lysis or lymphokine release (see, e.g., Kageyama et al., J. Immunol. 154:567-576, 1995).
- [00414] Atlernatively, immunogenicity can be evaluated through *in vivo* injections into mice and subsequent *in vitro* assessment of CTL and HTL activity, which are analysed using cytotoxicity and proliferation assays, respectively, as detailed *e.g.*, in copending U.S.S.N. 09/311,784 filed 5/13/99 and Alexander *et al.*, *Immunity* 1:751-761, 1994.
- [00415] For example, to assess the capacity of a DNA minigene construct (e.g., a pMin minigene construct generated as decribed in U.S.S.N. 09/311,784) containing at least one HLA-A2 supermotif peptide to induce CTLs in vivo, HLA-A2.1/Kb transgenic mice, for example, are immunized intramuscularly with 100 µg of naked cDNA. As a means of comparing the level of CTLs induced by cDNA immunization, a control group of animals is also immunized with an actual peptide composition that comprises multiple epitopes synthesized as a single polypeptide as they would be encoded by the minigene.
- [00416] Splenocytes from immunized animals are stimulated twice with each of the respective compositions (peptide epitopes encoded in the minigene or the polyepitopic peptide), then assayed for peptide-specific cytotoxic activity in a ⁵¹Cr release assay. The results indicate the magnitude of the CTL response directed against the A2-restricted epitope, thus indicating the *in vivo* immunogenicity of the minigene vaccine and polyepitopic vaccine. It is, therefore, found that the minigene elicits immune responses

directed toward the HLA-A2 supermotif peptide epitopes as does the polyepitopic peptide vaccine. A similar analysis is also performed using other HLA-A3 and HLA-B7 transgenic mouse models to assess CTL induction by HLA-A3 and HLA-B7 motif or supermotif epitopes.

[00417] To assess the capacity of a class II epitope encoding minigene to induce HTLs in vivo, DR transgenic mice, or for those epitope that cross react with the appropriate mouse MHC molecule, I-A^b-restricted mice, for example, are immunized intramuscularly with 100 μg of plasmid DNA. As a means of comparing the level of HTLs induced by DNA immunization, a group of control animals is also immunized with an actual peptide composition emulsified in complete Freund's adjuvant. CD4+ T cells, i.e. HTLs, are purified from splenocytes of immunized animals and stimulated with each of the respective compositions (peptides encoded in the minigene). The HTL response is measured using a ³H-thymidine incorporation proliferation assay, (see, e.g., Alexander et al. Immunity 1:751-761, 1994). The results indicate the magnitude of the HTL response, thus demonstrating the in vivo immunogenicity of the minigene.

DNA minigenes, constructed as described above or below, may also be evaluated as a vaccine in combination with a boosting agent using a prime boost protocol. The boosting agent can consist of recombinant protein (e.g., Barnett et al., Aids Res. and Human Retroviruses 14, Supplement 3:S299-S309, 1998) or recombinant vaccinia, for example, expressing a minigene or DNA encoding the complete protein of interest (see, e.g., Hanke et al., Vaccine 16:439-445, 1998; Sedegah et al., Proc. Natl. Acad. Sci USA 95:7648-53, 1998; Hanke and McMichael, Immunol. Letters 66:177-181, 1999; and Robinson et al., Nature Med. 5:526-34, 1999).

[00419] For example, the efficacy of the DNA minigene used in a prime boost protocol is initially evaluated in transgenic mice. In this example, A2.1/K^b transgenic mice are immunized IM with 100 μg of a DNA minigene encoding the immunogenic peptides including at least one HLA-A2 supermotif-bearing peptide. After an incubation period (ranging from 3-9 weeks), the mice are boosted IP with 10⁷ pfu/mouse of a recombinant vaccinia virus expressing the same sequence encoded by the DNA minigene. Control mice are immunized with 100 μg of DNA or recombinant vaccinia without the minigene sequence, or with DNA encoding the minigene, but without the vaccinia boost. After an additional incubation period of two weeks, splenocytes from the mice are immediately assayed for peptide-specific activity in an ELISPOT assay. Additionally, splenocytes are

stimulated *in vitro* with the A2-restricted peptide epitopes encoded in the minigene and recombinant vaccinia, then assayed for peptide-specific activity in an IFN- γ ELISA.

[00420] It is found that the minigene utilized in a prime-boost protocol elicits greater immune responses toward the HLA-A2 supermotif peptides than with DNA alone. Such an analysis can also be performed using HLA-A11 or HLA-B7 transgenic mouse models to assess CTL induction by HLA-A3 or HLA-B7 motif or supermotif epitopes.

[00421] The use of prime boost protocols in humans is described in below.

EXAMPLE 9. PEPTIDE COMPOSITION FOR PROPHYLACTIC USES

[00422] Vaccine compositions of the present invention can be used to prevent HIV infection in persons who are at risk for such infection. For example, a polyepitopic peptide epitope composition (or a nucleic acid comprising the same) containing multiple CTL and HTL epitopes, which are also selected to target greater than 80% of the population, is administered to individuals at risk for HIV infection.

[00423] For example, a peptide-based composition can be provided as a single polypeptide that encompasses multiple epitopes. The vaccine is typically administered in a physiological solution that comprises an adjuvant, such as Incomplete Freunds Adjuvant. The dose of peptide for the initial immunization is from about 1 to about 50,000 μg, generally 100-5,000 μg, for a 70 kg patient. The initial administration of vaccine is followed by booster dosages at 4 weeks followed by evaluation of the magnitude of the immune response in the patient, by techniques that determine the presence of epitope-specific CTL populations in a PBMC sample. Additional booster doses are administered as required. The composition is found to be both safe and efficacious as a prophylaxis against HIV infection.

[00424] Alternatively, a composition typically comprising transfecting agents can be used for the administration of a nucleic acid-based vaccine in accordance with methodologies known in the art and disclosed herein.

EXAMPLE 10. POLYEPITOPIC VACCINE COMPOSITIONS DERIVED FROM NATIVE HIV SEQUENCES

[00425] A native HIV polyprotein sequence is screened, preferably using computer algorithms defined for each class I and/or class II supermotif or motif, to identify "relatively short" regions of the polyprotein that comprise multiple epitopes and is preferably less in length than an entire native antigen. This relatively short sequence that contains multiple distinct, even overlapping, epitopes is selected and used to generate a minigene construct. The construct is engineered to express the peptide, which corresponds to the native protein sequence. The "relatively short" peptide is generally less than 250 amino acids in length, often less than 100 amino acids in length, preferably less than 75 amino acids in length, and more preferably less than 50 amino acids in length. The protein sequence of the vaccine composition is selected because it has maximal number of epitopes contained within the sequence, *i.e.*, it has a high concentration of epitopes. As noted herein, epitope motifs may be nested or overlapping, for example, two 9-mer epitopes and one 10-mer epitope can be present in a 10 amino acid peptide. Such a vaccine composition is administered for therapeutic or prophylactic purposes.

The vaccine composition will preferably include, for example, three CTL epitopes and at least one HTL epitope from HIV. This polyepitopic native sequence is administered either as a peptide or as a nucleic acid sequence which encodes the peptide. Alternatively, an analog can be made of this native sequence, whereby one or more of the epitopes comprise substitutions that alter the cross-reactivity and/or binding affinity properties of the polyepitopic peptide.

Undiscovered aspect of immune system processing will apply to the native nested sequence and thereby facilitate the production of therapeutic or prophylactic immune response-inducing vaccine compositions. Additionally such an embodiment provides for the possibility of motif-bearing epitopes for an HLA makeup that is presently unknown. Furthermore, this embodiment (absent analogs) directs the immune response to multiple peptide sequences that are actually present in native HIV antigens thus avoiding the need to evaluate any junctional epitopes. Lastly, the embodiment provides an economy of scale when producing nucleic acid vaccine compositions.

[00428] Related to this embodiment, computer programs can be derived in accordance with principles in the art, which identify in a target sequence, the greatest number of epitopes per sequence length.

EXAMPLE 11. POLYEPITOPIC VACCINE COMPOSITIONS DIRECTED TO MULTIPLE DISEASES

- [00429] The HIV peptide epitopes of the present invention are used in conjunction with peptide epitopes from target antigens related to one or more other diseases, to create a vaccine composition that is useful for the prevention or treatment of HIV as well as the one or more other disease(s). Examples of the other diseases include, but are not limited to, HCV and HBV.
- [00430] For example, a polyepitopic peptide composition comprising multiple CTL and HTL epitopes that target greater than 98% of the population may be created for administration to individuals at risk for both HBV and HIV infection. The composition can be provided as a single polypeptide that incorporates the multiple epitopes from the various disease-associated sources, or can be administered as a composition comprising one or more discrete epitopes.

EXAMPLE 12. USE OF PEPTIDES TO EVALUATE AN IMMUNE RESPONSE

- [00431] Peptides of the invention may be used to analyze an immune response for the presence of specific CTL or HTL populations directed to HIV. Such an analysis may be performed in a manner as that described by Ogg et al., Science 279:2103-2106, 1998. In the following example, peptides in accordance with the invention are used as a reagent for diagnostic or prognostic purposes, not as an immunogen.
- [00432] In this example highly sensitive human leukocyte antigen tetrameric complexes ("tetramers") are used for a cross-sectional analysis of, for example, HIV HLA-A*0201-specific CTL frequencies from HLA A*0201-positive individuals at different stages of infection or following immunization using an HIV peptide containing an A*0201 motif. Tetrameric complexes are synthesized as described (Musey et al., N. Engl. J. Med. 337:1267, 1997). Briefly, purified HLA heavy chain (A*0201 in this example) and β2-

microglobulin are synthesized by means of a prokaryotic expression system. The heavy chain is modified by deletion of the transmembrane-cytosolic tail and COOH-terminal addition of a sequence containing a BirA enzymatic biotinylation site. The heavy chain, β2-microglobulin, and peptide are refolded by dilution. The 45-kD refolded product is isolated by fast protein liquid chromatography and then biotinylated by BirA in the presence of biotin (Sigma, St. Louis, Missouri), adenosine 5'triphosphate and magnesium. Streptavidin-phycoerythrin conjugate is added in a 1:4 molar ratio, and the tetrameric product is concentrated to 1 mg/ml. The resulting product is referred to as tetramer-phycoerythrin.

[00433] For the analysis of patient blood samples, approximately one million PBMCs are centrifuged at 300 x g for 5 minutes and resuspended in 50 µl of cold phosphate-buffered saline. Tri-color analysis is performed with the tetramer-phycoerythrin, along with anti-CD8-Tricolor, and anti-CD38. The PBMCs are incubated with tetramer and antibodies on ice for 30 to 60 min and then washed twice before formaldehyde fixation. Gates are applied to contain >99.98% of control samples. Controls for the tetramers include both A*0201-negative individuals and A*0201-positive uninfected donors. The percentage of cells stained with the tetramer is then determined by flow cytometry. The results indicate the number of cells in the PBMC sample that contain epitope-restricted CTLs, thereby readily indicating the extent of immune response to the HIV epitope, and thus the stage of infection with HIV, the status of exposure to HIV, or exposure to a vaccine that elicits a protective or therapeutic response.

EXAMPLE 13. USE OF PEPTIDE EPITOPES TO EVALUATE RECALL RESPONSES

[00434] The peptide epitopes of the invention are used as reagents to evaluate T cell responses, such as acute or recall responses, in patients. Such an analysis may be performed on patients who have recovered from infection, who are chronically infected with HIV, or who have been vaccinated with an HIV vaccine.

[00435] For example, the class I restricted CTL response of persons who have been vaccinated may be analyzed. The vaccine may be any IIIV vaccine. PBMC are collected from vaccinated individuals and HLA typed. Appropriate peptide epitopes of the invention that, optimally, bear supermotifs to provide cross-reactivity with multiple HLA

supertype family members, are then used for analysis of samples derived from individuals who bear that HLA type.

- [00436] PBMC from vaccinated individuals are separated on Ficoll-Histopaque density gradients (Sigma Chemical Co., St. Louis, MO), washed three times in HBSS (GIBCO Laboratories), resuspended in RPMI-1640 (GIBCO Laboratories) supplemented with L-glutamine (2mM), penicillin (50U/ml), streptomycin (50 μg/ml), and Hepes (10mM) containing 10% heat-inactivated human AB serum (complete RPMI) and plated using microculture formats. A synthetic peptide comprising an epitope of the invention is added at 10 μg/ml to each well and HBV core 128-140 cpitope is added at 1 μg/ml to each well as a source of T cell help during the first week of stimulation.
- In the microculture format, 4 x 10⁵ PBMC are stimulated with peptide in 8 replicate cultures in 96-well round bottom plate in 100 μl/well of complete RPMI. On days 3 and 10, 100 ml of complete RPMI and 20 U/ml final concentration of rIL-2 are added to each well. On day 7 the cultures are transferred into a 96-well flat-bottom plate and restimulated with peptide, rIL-2 and 10⁵ irradiated (3,000 rad) autologous feeder cells. The cultures are tested for cytotoxic activity on day 14. A positive CTL response requires two or more of the eight replicate cultures to display greater than 10% specific ⁵¹Cr release, based on comparison with uninfected control subjects as previously described (Rehermann, et al., Nature Med. 2:1104,1108, 1996; Rehermann et al., J. Clin. Invest. 97:1655-1665, 1996; and Rehermann et al. J. Clin. Invest. 98:1432-1440, 1996).
- [00438] Target cell lines are autologous and allogeneic EBV-transformed B-LCL that are either purchased from the American Society for Histocompatibility and Immunogenetics (ASHI, Boston, MA) or established from the pool of patients as described (Guilhot, et al. J. Virol. 66:2670-2678, 1992).
- [00439] Cytotoxicity assays are performed in the following manner. Target cells consist of either allogeneic HLA-matched or autologous EBV-transformed B lymphoblastoid cell line that are incubated overnight with the synthetic peptide epitope of the invention at 10 μM, and labeled with 100 μCi of ⁵¹Cr (Amersham Corp., Arlington Heights, IL) for 1 hour after which they are washed four times with HBSS.
- [00440] Cytolytic activity is determined in a standard 4-h, split well ⁵¹Cr release assay using U-bottomed 96 well plates containing 3,000 targets/well. Stimulated PBMC are tested at effector/target (E/T) ratios of 20-50:1 on day 14. Percent cytotoxicity is determined from the formula: 100 x [(experimental release-spontaneous

release)/maximum release-spontaneous release)]. Maximum release is determined by lysis of targets by detergent (2% Triton X-100; Sigma Chemical Co., St. Louis, MO). Spontaneous release is <25% of maximum release for all experiments.

[00441] The results of such an analysis indicate the extent to which HLA-restricted CTL populations have been stimulated by previous exposure to HIV or an HIV vaccine.

[00442] The class II restricted HTL responses may also be analyzed. Purified PBMC arc cultured in a 96-well flat bottom plate at a density of 1.5x10⁵ cells/well and are stimulated with 10 μg/ml synthetic peptide, whole antigen, or PHA. Cells are routinely plated in replicates of 4-6 wells for each condition. After seven days of culture, the medium is removed and replaced with fresh medium containing 10U/ml IL-2. Two days later, 1 μCi ³H-thymidine is added to each well and incubation is continued for an additional 18 hours. Cellular DNA is then harvested on glass fiber mats and analyzed for ³H-thymidine incorporation. Antigen-specific T cell proliferation is calculated as the ratio of ³H-thymidine incorporation in the presence of antigen divided by the ³H-thymidine incorporation in the absence of antigen.

EXAMPLE 14. INDUCTION OF SPECIFIC CTL RESPONSE IN HUMANS

[00443] A human clinical trial for an immunogenic composition comprising CTL and HTL epitopes of the invention is set up as an IND Phase I, dose escalation study and carried out as a randomized, double-blind, placebo-controlled trial. Such a trial is designed, for example, as follows:

[00444] A total of about 27 subjects are enrolled and divided into 3 groups:

Group I: 3 subjects are injected with placebo and 6 subjects are injected with 5 μg of peptide composition;

Group II: 3 subjects are injected with placebo and 6 subjects are injected with 50 µg peptide composition;

Group III: 3 subjects are injected with placebo and 6 subjects are injected with 500 μ g of peptide composition.

[00445] After 4 weeks following the first injection, all subjects receive a booster inoculation at the same dosage.

- [00446] The endpoints measured in this study relate to the safety and tolerability of the peptide composition as well as its immunogenicity. Cellular immune responses to the peptide composition are an index of the intrinsic activity of this the peptide composition, and can therefore be viewed as a measure of biological efficacy. The following summarize the clinical and laboratory data that relate to safety and efficacy endpoints.
- [00447] Safety: The incidence of adverse events is monitored in the placebo and drug treatment group and assessed in terms of degree and reversibility.
- [00448] Evaluation of Vaccine Efficacy: For evaluation of vaccine efficacy, subjects are bled before and after injection. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.
- [00449] The vaccine is found to be both safe and efficacious.

EXAMPLE 15. PHASE II TRIALS IN PATIENTS INFECTED WITH HIV

- [00450] Phase II trials are performed to study the effect of administering the CTL-HTL peptide compositions to HIV-infected patients. The main objectives of the trials are to determine an effective dose and regimen for inducing CTLs in chronically infected HIV patients, to establish the safety of inducing a CTL and HTL response in these patients, and to see to what extent activation of CTLs improves the clinical picture of chronically infected HIV patients, as manifested by a reduction in viral load and an increase in CD4⁺ cells counts. Such a study is designed, for example, as follows:
- [00451] The studies are performed in multiple centers. The trial design is an open-label, uncontrolled, dose escalation protocol wherein the peptide composition is administered as a single dose followed six weeks later by a single booster shot of the same dose. The dosages are 50, 500 and 5,000 micrograms per injection. Drug-associated adverse effects (severity and reversibility) are recorded.
- [00452] There are three patient groupings. The first group is injected with 50 micrograms of the peptide composition and the second and third groups with 500 and 5,000 micrograms of peptide composition, respectively. The patients within each group range in age from 21-65, include both males and females, and represent diverse ethnic

backgrounds. All of them are infected with HIV for over five years and are HCV, HBV and delta hepatitis virus (HDV) negative, but have positive levels of HIV antigen.

[00453] The viral load and CD4⁺ levels are monitored to assess the effects of administering the peptide compositions. The vaccine composition is found to be both safe and efficacious in the treatment of HIV infection.

EXAMPLE 16. INDUCTION OF CTL RESPONSES USING A PRIME BOOST PROTOCOL

[00454] A prime boost protocol can also be used for the administration of the vaccine to humans. Such a vaccine regimen can include an initial administration of, for example, naked DNA followed by a boost using recombinant virus encoding the vaccine, or recombinant protein/polypeptide or a peptide mixture administered in an adjuvant.

[00455] For example, the initial immunization is performed using an expression vector, such as that constructed above, in the form of naked nucleic acid administered IM (or SC or ID) in the amounts of 0.5-5 mg at multiple sites. The nucleic acid (0.1 to 1000 μg) can also be administered using a gene gun. Following an incubation period of 3-4 weeks, a booster dose is then administered. The booster is, for example, recombinant fowlpox virus administered at a dose of 5-10⁷ to 5x10⁹ pfu. An alternative recombinant virus, such as an MVA, canarypox, adenovirus, or adeno-associated virus, can also be used for the booster, or the polyepitopic protein or a mixture of the peptides can be administered. For evaluation of vaccine efficacy, patient blood samples are obtained before immunization as well as at intervals following administration of the initial vaccine and booster doses of the vaccine. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.

[00456] Analysis of the results indicates that a magnitude of sufficient response to achieve protective immunity against HIV is generated.

EXAMPLE 17. ADMINISTRATION OF VACCINE COMPOSITIONS USING DENDRITIC CELLS

[00457] Vaccines comprising peptide epitopes of the invention can be administered using APCs, or "professional" APCs such as DC. In this example, the peptide-pulsed DC are administered to a patient to stimulate a CTL response in vivo. In this method, dendritic cells are isolated, expanded, and pulsed with a vaccine comprising peptide CTL and HTL epitopes of the invention. The dendritic cells are infused back into the patient to elicit CTL and HTL responses in vivo. The induced CTL and HTL then destroy or facilitate destruction of the specific target cells that bear the proteins from which the epitopes in the vaccine are derived.

[00458] For example, a cocktail of epitope-bearing peptides is administered ex vivo to PBMC, or isolated DC therefrom. A pharmaceutical to facilitate harvesting of DC can be used, such as ProgenipoietinTM (Monsanto, St. Louis, MO) or GM-CSF/IL-4. After pulsing the DC with peptides and prior to reinfusion into patients, the DC are washed to remove unbound peptides.

[00459] As appreciated clinically, and readily determined by one of skill based on clinical outcomes, the number of DC reinfused into the patient can vary (see, e.g., Nature Med. 4:328, 1998; Nature Med. 2:52, 1996 and Prostate 32:272, 1997). Although 2-50 x 10⁶ DC per patient are typically administered, larger number of DC, such as 10⁷ or 10⁸ can also be provided. Such cell populations typically contain between 50-90% DC.

In some embodiments, peptide-loaded PBMC are injected into patients without purification of the DC. For example, PBMC containing DC generated after treatment with an agent such as Progenipoietin™ are injected into patients without purification of the DC. The total number of PBMC that are administered often ranges from 10⁸ to 10¹⁰. Generally, the cell doses injected into patients is based on the percentage of DC in the blood of each patient, as determined, for example, by immunofluorescence analysis with specific anti-DC antibodies. Thus, for example, if Progenipoietin™ mobilizes 2% DC in the peripheral blood of a given patient, and that patient is to receive 5 x 10⁶ DC, then the patient will be injected with a total of 2.5 x 10⁸ peptide-loaded PBMC. The percent DC mobilized by an agent such as Progenipoietin™ is typically estimated to be between 2-10%, but can vary as appreciated by one of skill in the art.

Ex vivo activation of CTL/HTL responses

[00461] Alternatively, ex vivo CTL or HTL responses to HIV antigens can be induced by incubating in tissue culture the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of APC, such as DC, and the appropriate immunogenic peptides. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused back into the patient, where they will destroy or facilitate destruction of their specific target cells.

[00462] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, patent applications and sequence listings cited herein are hereby incorporated by reference in their entirety for all purposes.

TABLE 1

SUPERMOTIFS	POSITION	POSITION	POSITION
	2 (Primary	3 (Primary	C Terminus (Primary
	Anchor)	Anchor)	Anchor)
Al	T, I, L, V, M, S		F, W, Y
A2	L, I, V, M, A, T, Q		I, V, M, A, T, L
A3	V, S, M, A, T, L,		R,K
A24	Y, F, W, I, V, L, M, T		F, I, Y, W, L, M
B7	P		V, I, L, F, M, W, Y, A
B27	R, H, K		F, Y, L, W, M, I, V, A
B44	\mathbf{E}, D		F, W, L, I, M, V, A
B58	A, T, S		F, W, Y, L, I, V, M, A
B62	Q, L, I, V, M, P		F, W, Y, M, I, V, L, A
MOTIFS		ļ <u> </u>	
Al	T, S, M	 	Y
Al	1,5,1,1	D, E, A, S	Y
A2.1	L, M, V, Q, I, A,	2, 2, 11, 5	V, L, I, M, A, T
A3	L, M, V, I, S, A, T, F, C, G, D		K, Y, R, H, F, A
A11	V, T, M, L, I, S, A, G, N, C, D, F		K, R, Y, H
A24	Y, F, W, M		F, L, I, W
A*3101	M, V, T, A, L, I,		R, K
A*3301	M, V, A, L, F, I, S, T		R, K
A*6801	A, V, T, M, S, L,		R, K
B*0702	P		L, M, F, W, Y, A, I, V
B*3501	P	 	L, M, F, W, Y, I, V, A
B51	P		L, I, V, F, W, Y, A, M
B*5301	P		I, M, F, W, Y, A, L, V
B*5401	P	·	A, T, I, V, L, M, F, W,

Bolded residues are preferred, italicized residues are tolerated: A peptide is considered motif-bearing if it has primary anchors at each primary anchor position for a motif or supermotif as specified in the above table.

TABLE 2

SUPERMOTIFS	POSITION	POSITION	POSITION
	2 (Primary	3 (Primary	C Terminus (Primary
	Anchor)	Anchor)	Anchor)
A1	T , I , <i>L</i> , <i>V</i> , <i>M</i> , <i>S</i>		F, W, Y
A2	V, Q, A, T	7 .//	I, V, L, M, A, T
A3	V, S, M, A, T, L,		R, K
A24	Y, F, W, I, V, L, M, T		F, I, Y, W, L, M
B7	P		V, I, L, F, M, W, Y, A
B27	R, H, K		F, Y, L, W, M, I, V, A
B58	A, T, S		F, W, Y, L, I, V, M, A
B62	Q , L, <i>I</i> , <i>V</i> , <i>M</i> , <i>P</i>		F, W, Y, M, I, V, L, A
MOTIFS			
Ai	T, S, M	<u> </u>	Y
A1		D, E, <i>A</i> , <i>S</i>	Y
A2.1	V, Q, A, T*	, , , , ,	V, L, I, M, A, T
A3.2	L, M, V, I, S, A,		K, Y, R, H, F, A
	T, F, C, G, D		, -,, -1, 11
A11	V, T, M, L, I, S,		K, R, H, Y
	A, G, N, C, D, F] , = , = , =
A24	Y,F,W		F, L, I, W

^{*}If 2 is V, or Q, the C-term is not L

Bolded residues are preferred, italicized residues are tolerated: A peptide is considered motif-bearing if it has primary anchors at each primary anchor position for a motif or supermotif as specified in the above table.

TABLE 3

C-terminus		1° Anchor F, W, Y	l° Anchor L,1,V,M,A,T	1°Anchor R,K		1° Anchor F,1, Y, W,L,M	1°Anchor V,I,L,F,M,W,Y,A		1° Anchor F,Y,L,W,M,V,A	N. Anchor F,W,Y,L,I,M,V,A
œ.				Y,F,W, (4/5) P, (4/5)			F,W,Y, (3/5)	5) D,E, (4/5)		
				Y,F,W,				Q,N, (4/5)		
ION 6				Y,F,W, (3/5)				G, (4/5)		
POSITION [5]								D,E, (3/5)		
4										
<u></u>				Y,F,W, (4/5)	D,E, (4/5)		F,W,Y (4/5)			
<u>(</u>		1° Anchor T,I,L, V,M,S	1° Anchor L,I,V,M,A, T,O	1° Anchor V,S,M,A,T, L,I		I° Anchor Y,F,W,I,V, L,M,T	1°Anchor P		1° Anchor R,H,K	l° Anchor E,D l° Anchor
					D,E (3/5); P, (5/5)		F,W,Y (5/5) L,I,V,M, (3/5)	D,E (3/5); P(5/5); G(4/5); A(3/5); Q,N, (3/5)		
	SUPERMOTIFS			ргебетед	deleterious		preferred	deleterious		
	SUPE	A1	A2	A3		A24	B7		B27	B44

TABLE 3 (Continued)

Harden 12-Anchor 12-Anch			1	হো	<u>.</u>	4	POSITION [5]			<u>∞</u> 1	9 C- or termin C-terminus us
PS Preference Properties Properties	B58			A,T,S							F,W,Y,L,I,V,M,A
FS Preferred G,F,Y,W, 1ºAnchor S,T,M, D,E,A, Y,F,W, P, D,E,Q,N, deleterious D,E, R,H,K,L,I,V A, G, A, preferred G,R,H,K A,S,T,C,L,I 1ºAnchor V,M, G,S,T,C, A,S,T,C, L,I,V,M, deleterious A R,H,K,D,E, D,E,A,S, D,E, P,Q,N, R,H,K, P,G, peferred Y,F,W, 1ºAnchor D,E,A,Q,N, A, Y,F,W,Q,N, P,A,S,T,C, C,I,I,V,M, deleterious G,P, R,H,K,G,L,I D,E, R,H,K,Q,N, R,H,K,Y,F, R,H,K,Y,F,	B62		·	1º Anchor Q,L,I,V,M, P							1° Anchor F, W, Y, M.I. V. L. A
preferred G,F,Y,W, S,T,M, S,T,M, 19-Anchor S,T,M, S,T,M, D,E,A,S,T,C,L,I Y,F,W, M, B,E,A,S Y,F,W, M, B,E,A,S Y,F,W, M, B,E,A,S Y,F,W, M, B,E,A,S,T,C, L,I,V,M, B,E,A,S,T,C, B,E,A,S,T,C, B,E,A,Q,N, B,E,W,Q,N, B,H,K,Y,F, B,E,A,S,T,C, S,T,M,	MOTI	SI									
deleterious D,E, M,P, M,P, R,H,K,L,I,V M,P, A, G, G,S,T,C, D,E,A,S G,S,T,C, A,S,T,C,C, D,E,A,S A, S,T,C, B,E,A,S A, S,T,C, B,E,A,S A, S,T,C, B,E,A,S A, S,T,C, B,E,A,S A, S,T,C, B,E,A,S A, S,T,C, B,E,A,S B,E,A,C, B,E,A,C,B, B,E,A,C,B, B,E,A,C,B, B,E,A,C,B, B,E,A,C,B, B,E,A,C,B, B,E,A,C,B, A, E,E,W,C,B, B,E,E,W,C,B, B,E,A,C,B,B, B,E,B,E,B,B,B,B,B,B,B,B,B,B,B,B,B,	A1 9-mer	ргебепед	G,F,Y,W,	L'Anchor S,T,M,	D,E,A,	Y,F,W,		ď.	D,E,Q,N,	Y,F,W,	1. Anchor Y
preferred G,R,H,K A,S,T,C,L,I 1°Anchor D,E,A,S G,S,T,C, A,S,T,C, deleterious A R,H,K,D,E, P,Y,F,W, D,E,A,Q,N, B,C,N, R,H,K, deleterious G,P, R,H,K,G,L,I D,E,A,Q,N, A, Y,F,W,Q,N, deleterious G,P, R,H,K,G,L,I D,E, R,H,K, Q,N,A	i	deleterious	Ď,Ē,		R,H,K,L,I,V M,P,	Α,	ڻ ن	Ą			
preferred G,R,H,K A,S,T,C,L,I L'Anchor D,E,A,S G,S,T,C, A,S,T,C, deleterious A R,H,K,D,E, P,Y,F,W, D,E,A,Q,N, B,E,A,Q,N, R,H,K, peferred Y,F,W, L'Anchor D,E,A,Q,N, A, Y,F,W,Q,N, deleterious G,P, R,H,K,G,L,I D,E, R,H,K, Q,N,A											
deleterious A R,H,K,D,E, W, D,E,A,Q,N, A, Y,F,W,Q,N, R,H,K,G,L,I D,E,A,Q,N, A, Y,F,W,Q,N, B,H,K,G,L,I D,E,A,Q,N, A, H,K,G,L,I B,E,B,K,C,M,	A1 9-mer	ргебетед	G,R,H,K	A,S,T,C,L,I V,M,		G,S,T,C,		A,S,T,C,	L,I,V,M,	D,E,	1°Anchor Y
peferred Y,F,W, 1ºAnchor D,E,A,Q,N, A, Y,F,W,Q,N, S,T,M S,T,M R,H,K,G,L,I D,E, R,H,K, Q,N,A V,M,		deleterious	۷ .	R,H,K,D,E, P,Y,F,W,		D,E,	P,Q,N,	R,H,K,	P,G,	G,P,	
G,P, R,H,K,G,L,I D,E, R,H,K, Q,N,A V,M,	A1 10-mer	peferred	Y,F,W,	1°Anchor S,T,M	D,E,A,Q,N,	Α,	Y,F,W,Q,N,		P,A,S,T,C,	G,D,E,	P, <u>1°Anchor</u>
		deleterious	G,P,		R,H,K,G,L,I V,M,	D,E,	R,H,K,	Q,N,A	R,H,K,Y,F, W,	R,H,K,	V

TABLE 3 (Continued)

TABLE 3 (Continued)

A3101 preferred R,H,K, 1ºAnchor Y,F,W, P, Y,F,W, Y,F,W, A,P, 1ºAnchor M,V,T,A,L,

TABLE 3 (Continued)

	ن .	rermin us									
	6	or C-terminus		1°Anchor R,K		1°Anchor R,K		1°Anchor L,M,F, <i>W,Y,A</i> ,	٠.	1ºAnchor L,M,F,W,Y,,	
	<u></u>		D,E,			e.'	ť	P,A,	D,E,		
			D,E,	A,Y,F,W		Y,F,W,		R,H,K,	Ö,	F,W,Y,	
NO	9		D,E,					R,H,K,	G,D,E,		ზ
POSITION	ટ		A,D,E,			Y,F,W,L,I, V,M	R,H,K,	R,H,K,	D,E,		ზ _
	4							·	D,E,		
	<u></u>		D,E,	Y,F,W	D,E		D,E,G,	R,H,K,	D,E,P,	F, W, Y,	
	ලා			1°Anchor M,V,A,L,F, <i>I,S,T</i>		l°Anchor A,V,T,M,S, L,I		l°Anchor P		<u>1°Anchor</u> P	
	—)		D,E,P,		G,P	Y,F,W,S,T,C,	G,P,	R,H,K,F,W,Y,	D,E,Q,N,P,	F,W,Y,L,I,V,M,	A,G,P,
			S	A3301 preferred	deleterious	A6801 preferred	defeterious	B0702 preferred	deleterious	B3501 preferred	deleterious
				A3301		A6801		B0702	į	B3501	

TABLE 3 (Continued)

					ı		1	
(C- termin	sn						
Ē	a 5	C-terminus	L,I,V,F,W,		1°Anchor I,M,F,W,Y,		1°Anchor A,T,I,V,L,	
	<u></u>		F,W,Y,	G,D,E,	F,W,Y,	D,E,	F,W,Y,A,P, 1°Anchor A,T,I,V,L,	D,E,
Œ	5)		ර	D,E,Q,N,	L,I,V,M,F, W,Y,	R,H,K,Q,N, D,E,	A,L,I,V,M,	Q,N,D,G,E, D,E,
ION	0			ပ်		ڻ ن		, D,E,
POSITION	<u> </u>		F,W,Y,	D,E,	F,W,Y,		L,I,V,M,	R,H,K,D,E, D,E,
	1]		S,T,C,		S,T,C,			
[6	ച		F,W,Y,		F,W,Y,		F,W,Y,L,I,V M,	G,D,E,S,T,C,
IZ.	2 D		1°Anchor P		l°Anchor P		1°Anchor P	
11	.		L,I,V,M,F,W,Y,	A,G,P,D,E,R,H,K, S,T,C,	L,I,V,M,F,W,Y,	A,G,P,Q,N,	F,W,Y,	G,P,Q,N,D,E,
			preferred	deleterious	B5301 preferred	deleterious	B5401 preferred	deleterious
			B51		B5301		B5401	

Italicized residues indicate "tolerated" residues.

The information in Table II is specific for 9-mers unless otherwise specified.

Secondary anchor specificities are designated for each position independently.

Table 4

B*1301, B*1302, B*1504, B*1505, B*1506, B*1507,	B*1501, B*1502, B*1513, B*5201	B62
	B*1517	
	B*5701, B*5702, B*5801, B*5802, B*1516,	B58
	B*4404, B*4001, B*4002, B*4006	
B*4101, B*4501, B*4701, B*4901, B*5001	B*1801, B*1802, B*3701, B*4402, B*4403,	B44
B*3905, B*4801, B*4802, B*1510, B*1518, B*1503	B*2704, B*2705, B*2706, B*3801, B*3901, B*3902, B*7301	
B*2701, B*2707, B*2708, B*3802, B*3903, B*3904	B*1401, B*1402, B*1509, B*2702, B*2703,	B27
	B*7801	
	B*5301, B*5401, B*5501, B*5502, B*5601, B*5602, B*6701,	
	B*3507, B*3508, B*5101, B*5102, B*5103, B*5104, B*5105,	
	B*3501, B*3502, B*3503, B*3503, B*3504, B*3505, B*3506,	
B*1511, B*4201, B*5901	B*0702, B*0703, B*0704, B*0705, B*1508,	В/
A*2403, A*2404, A*3002, A*3003	A+2301, A+2402, A+3001	724
A*3402, A*6601, A*6602, A*7401	******	100
A*0302, A*1102, A*2603, A*3302, A*3303, A*3401,	A*0301, A*1101, A*3101, A*3301, A*6801	AS
	A*0206, A*0207, A*0209, A*0214, A*6802, A*6901	
A*0208, A*0210, A*0211, A*0212, A*0213	A*0201, A*0202, A*0203, A*0204, A*0205,	AZ
A*0102, A*2604, A*3601, A*4301, A*8001	A*0101, A*2501, A*2601, A*2602, A*3201	AI .
Fredicted	4 6111160	4.1
j	Verified	HLA-supertype

- a of the sequences of CTL epitopes. Verified alleles include alleles whose specificity has been determined by pool sequencing analysis, peptide binding assays, or by analysis
- Ġ specificity. Predicted alleles are alleles whose specificity is predicted on the basis of B and F pocket structure to overlap with the supertype

4.5 H O E Z 1.0 2.8 4.2 4.7 4.7 6.3 G 1.0 3.8 4.3 6.2 6.7 Σ 1.0 3.5 4.0 6.2 O Z H O ပ 4

Table 5. Compiled rankings and similarity assignments.

Conserved (1-7)

Non-conserved (13.1-20)

6.3 æ 0.9 Σ

Table 5 (continued)

Non-conserved (13.1-20)

Semi-conserved (7.1-13)

Conserved (1-7)

127

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Table 6. Recognition of variant peptides by CTL generated after one and five stimulations with the parent peptide.

A. Gaq	386	(VLAEAMSQV)
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	Binding	1 Stimulation	5 Stimulations
Peptide Sequence	IC50 (nM)	(SU)	(SU)
VLAEAMSQV	49.9	31.6	222.0
VLAEAMSQA	23.8	17.0	133.5
VLAEAMSQI	70.9	21.2	246.1
VLAEAMSKV	230.5	10.8	130.9
VLAEAMS KA	69.4	NT	36.6
ILAEAMSQA	29.3	4.0	49.7
ILAEAMSKA	72.4		
VLAEAMAAA	17	16.3	90.3

B. Env 134 (F	(LTPLCVTL)
---------------	------------

	· · - /		
KLTPLCVTL	77.0	278.4	683.6
KITPLCVTL	461	231.8	700.8
QLTPLCVTL	63.6	166.2	361.5
QITPLCVTL	975	105.0	166.9
ELTPLCVTL	7190	.91.7	100.0
KLTPFCVTL	87.3	36.1	75.4
KLTPLCVIL	356	77.2	29.1
KLTPLCVPL	14.6	9.6	14.8

. Table 7. Conservation of EP HIV-1090 epitopes across clades, calculated as identity or immunological conservation

			Tatal			_	
Dentain	0		<u>Total</u>	<u>C</u>	lade B	<u>c</u>	lade C
Protein	Sequence	Identity	Imm. Cons.	Identity	Imm. Cons.	Identity	Imm. Cons.
Pol 498	ILKEPVHGV	62%	87%	77%	86%	74%	95%
Gag 386	VLAEAMSQV	32%	93%	68%	91%	5%	94%
Pol 448	KLVGKLNWA	95%	96%	95%	95%	95%	98%
Env 134	KLTPLCVTL	80%	93%	90%	95%	89%	98%
Vpr 62	RILQQLLFI	51%	93%	68%	91%	61%	95%
Nef 221	LTFGWCFKL	49%	74%	77%	91%	47%	81%
Gag 271	MTNNPPIPV	20%	25%	91%	95%	8%	19%
Env 47	VTVYYGVPVWK	59%	87%	95%	100%	61%	92%
Pol 929	QMAVFIHNFK	84%	98%	100%	100%	94%	97%
Pol 98	 VTIKIGGQLK 	11%	71%	59%	91%	2%	89%
Pol 971	KIQNFRVYYR	80%	86%	91%	95%	79%	89%
Pol 347	AIFQSSMTK	53%	75%	77%	82%	44%	79%
Pol 722	KVYLAWVPAHK	14%	97%	82%	95%	3%	97%
Env 61	TTLFCASDAK	72%	89%	90%	100%	69%	92%
Nef 94	FPVRPQVPL	81%	93%	77%	95%	82%	94%
Gag 545	YPLASLRSLF	7%	29%	45%	95%	0%	0%
Rev 75	VPLQLPPL	44%	78%	68%	77%	27%	79%
Env 259	IPIHYCAPA	74%	95%	45%	95%	79%	97%
Gag 237	HPVHAGPIA	27%	54%	68%	95%	44%	94%
Pol 893	IPYNPQSQGVV	92%	96%	82%	95%	240%	97%
Env 250	CPKVSFEPI	45%	91%	77%	100%	45%	97%
	Mean	54%	81%	77%	93%	59%	84%
	n=	167		22		62	

					<u> </u>			
1		·		uence				
			Distr					
Protein	Sequence	Consomi			уре	· -:		
riotern	sequence	Conserved Epitopes*	All	A	B	C	D	G
Pol 498	ILKEPVHGV	ILKEPVHGV	104	$+_1$	17	46		-
		ILREPVHGV	12	1-	1/	5	_2	1
		ILKEPVHGA	10	+	 	2	1	
		ILKDPVHGV	8	5				
		KLKEPVHGV	3	+-		 		├
		ILKDPVHGA	2	2				
		ILKNPVHGV	2	† -	ļ —			╫
						-		
Gag 386	VLAEAMSQV	VLABAMSQA	67	2	1	36	3	3
		VLAEAMSQV	54	7	15	3	1	
		VLAEAMSQT	11			9		
		VLAEAMSHA	6			4		
		ILAEAMSQV	5		3			
		ILAEAMSQA	3			2		
		VLAEAMSHV	2					
7 110								
Pol 448	KLVGKLNWA	KLVGKLNWA	158	9	21	59	3	3
		KLIGKLNWA	1	╀				<u>L</u>
Env 134	KLTPLCVTL	PT TOT CTUTE	124	-				<u> </u>
CIIV 134	KUIPUCVIU	KLTPLCVTL	134	8	19	55	<u> </u>	
	•	QLTPLCVTL	5	2	1			_
		KLTPLCVAL	3					<u> </u>
		RLTPLCVTL KITPLCVTL	3 2			3		_
		KITPUCVID	2	 	 			
Vpr 62	RILQQLLFI	RILQQLLFI	86	$+_{i}$	15	28	4	3
		RILQQLLFV	21	- 2		2		-3
		RTLQQLLFI	10	├ ~	2	4		├-
		RTLQQLLFV	10			1		
		RILQQLLFT	6	+		2		
		RMLQQLLFI	4	1	1	3		-
		RVLQQLLFI	3			3		<u> </u>
Nef 221	LTFGWCFKL	LTPGWCFKL	82	8	17	29		3
		LTFGWCYKL	31	1	2	17		
		LTLGWCFKL	4			1		
T								
	•		1		i	!		
į			Ī	1	1			ı

Gag 271	MTNNPPIPV	MTSNPPIPV	T 60	3		124		T
		MTNNPPIPV	33	1	20	24 5	4	1
		MTSNPPVPV	26	1	20		 	
		MTGNPPIPV	15	5		15	 	1
		MTGNPPVPV	9	1-3-	ļ	1	 	├
		MTNNPPVPV	6 .	- -		5	 	├ ──
		MTANPPVPV	3	┨		6		<u> </u>
			- - -				<u> </u>	
Env 47	VTVYYGVPVWK	VTVYYGVPVWK	99	6	21	30	3	-
		VTVYYGVPVWR	40	1		18	<u> </u>	├
		VTIYYGVPVWK	2	 			-	├─
				1		 	 	
Pol 929	QMAVFIHNFK	QMAVFIHNFK	153	10	22	58	4	3
		QMAVFVHNFK	3			1		
		QMAVFVHNYK	2			 		
	,,,,,						<u> </u>	
Pol 98	VTIKIGGQLK	VSIKVGGQIK	30	1		30		
		VTIKIGGQLK	18		13	1	 	ļ
		VTVKIGGQLK	11	1	1		1	
		VTVRIGGQLK	6	3				
		VSIKVGGQIR	6			6		
	· · · · · · · · · · · · · · · · · · ·	VSIRVGGQIK	4			4		
		VTIRIGGQLK	3		2			
		VTVKIGGQLR	3	1		 -		
		VTVKVGGQLK	3					
Pol 971	KIQNFRVYYR	KIQNFRVYYR	133	6	20	49	4	3
Pol 347	AIFQSSMTK	AIFQSSMTK	00					
	TITI QUUNTIK		.88	5	17	27	3	2
		AIFQCSMTK	19		2	5		
		AIFOSSMTR	13		1_	11		1
		AIFQASMTK SIFQSSMTK	9	1		1		
		AIFQYSMTK	9	3		6		
		AIFQSTMTK	4					
	•	TILASIMIK	2			1		
Pol 722	KVYLAWVPAHK	KVYLSWVPAHK	56	8		12	_	3
		RVYLSWVPAHK	55			41		
		KVYLAWVPAHK	23	1	10	4.1		
		KVYLTWVPAHK	5	1	18		3	
		KIYLSWVPAHK	5			3		<u> </u>
		RIYLSWVPAHK	5	├		4		•
		KIYLAWVPAHK	2	 	1	-		
		QVYLTWVPAHK	2	 				
								
Ì								

	1							
Env 61	TTLFCASDAK	TTLFCASDAK	121	9	19	41	4	1
		ATLFCASDAK	7		_	7	 - -	+
•		TILFCASDAK	6		1	╅	+	+-
		PTLFCASDAK	2	\top	 	1	 	+
		TTLFCASDAR	2		2	 -	 	+-
		TTLFCASEAK	2	1	1	\dagger	1	+
		ATLFCASDAR	2		1	1 2		+
						1	†	+
Nef 94	FPVRPQVPL	FPVRPQVPL	135	8	17	51	4	3
		FPVKPQVPL	9	1	3	2	+	
		FPVRPQVPV	4		1	2	 -	+-
				-			 	+
Gag 545	YPLASLRSLF	EPLTSLKSLF*	22			21		+
		YPLASLKSLF*	13	1	5	 	2	
*These	two would not be	predicted to XI	R. Would	cho	ose	both	 -	+
to get i	maximal populati	on coverage.					1	
		YPLASLRSLF	11		10	Τ.	 	
		YPLTSLKSLF	10		1		2	1
		YPPLASLKSL	10				_	1-
		YPLTSLRSLF	6		4			_
		YPPLTSLKSL	6		-			
D DE								1
Rev 75	VPLQLPPL	VPLQLPPL	64	5	15	7	4	2
		VPLQLPPI	34	2	1	19	 	1
		VPFQLPPI	26			23	\vdash	
		VPFQLPPL	3		1			1
								 -
Env 259	IPIHYCAPA	IPIHYCAPA	124	8	10	49	3	2
		IPIHYCTPA	25	1	8	8		
·		IPIHFCAPA	3		1	1	1	
Gag 237	HPVHAGPIA	HPVHAGPIA	39		15	21	1	
	i	HPVHAGPVA					 _	 -
	·	VILLOI VA	34	1	3	27	1 2	
		HPVQAGPVA	34 12	1	3		2	
				1		6	1	
		HPVQAGPVA	12	1		6		
Pol 893	IPYNPQSQGVV	HPVQAGPVA	12	9		6	1	3
Pol 893	IPYNPQSQGVV	HPVQAGPVA HPIHAGPIA	12		3	6		3
Pol 893	IPYNPQSQGVV	HPVQAGPVA HPIHAGPIA IPYNPQSQGVV	12 2 153		18	60	1	3
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV	12 2 153 5		18	6	1	3
Pol 893	I PYNPQSQGVV CPKVSFEPI	HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI	12 2 153 5		18	60	1	3
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV	12 2 153 5 2	9	18	60	4	
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV CPKVSFEPI	12 2 153 5 2	9	18	60 60 1 3 33	4	0
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV CPKVSFEPI CPKVSFDPI	12 2 153 5 2 50 42 16	9	18	60 1 3 33 13	4	0
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV CPKVSFEPI CPKVSFDPI CPKVTFDPI	12 2 153 5 2 50 42 16 13	9	18	60 1 3 33 13	4	0
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV CPKVSFEPI CPKVSFDPI CPKVTFDPI CPKVTFEPI CPKISFDPI	12 2 153 5 2 50 42 16 13 9	9	18 3 	60 1 3 33 13	2	0
		HPVQAGPVA HPIHAGPIA IPYNPQSQGVV IPYNPQSQGVI IPYNPQSQGAV CPKVSFEPI CPKVSFDPI CPKVTFDPI CPKVTFEPI	12 2 153 5 2 50 42 16 13	9	18	60 1 3 33 13	4	0

£0450026.032803

Source	HPV peptide	HPV			 	
Dource	Sequence	Strain	Variant	SEQ ID		Measured
	bequence	SCLAIM	Sequences	МО	Immunogenicity	
HPV16.E7.86	TLGIVCPI	16	MY CITYLE	 		city (SU)
120.87.00	IBGIVEPI	16	TLGIVCPI	 	+	103.7
		31	TLSFVCPW	 	-	
		33	SFGIVCPN		-	
		45	TVNIVCPT TLSFVCPW		-	
		52	TLQVVCPG		-	
		56	ALTVTCPL		-	
		58	TCTIVCPS	 		<u>.</u>
			TCTTVCPS	 		
HPV31.E6.11	KLHELSSAL	16	KLPQLCTEL	 		
		18	KLPDLCTEL	 		
		31	KLHELSSAL	 		
		33	TLHDLCQAL	 		26.3
		45	KLPDLCTEL	 		
		52	TLHELCEVL	 		
		56	SLHHLSEVL	T		
		58	TLHDLCQAL			
HPV18/45.E6 .13	KLPDLCTEL	16	KLPQLCTEL		+	15.7
		. 18	KLPDLCTEL		+	212.7
		31	KLHELSSAL			212.7
		33	TLHDLCQAL			
		45	KLPDLCTEL		+	205.1
		52	TLHELCEVL		_	203.1
		56	SLHHLSEVL		-	
		58	TLHDLCQAL			
IDVED DC 10						
IPV52.E618	VLEESVHEI	16	ELQTTIHDI		-	
		18	ELNTSLQDI		-	
		31	ALEIPYDEL		_	
		33	ALETTIHNI		_	
		45	ELNTSLQDV		-	
		52	VLEESVHEI		+	64.1
		56	VLEIPLIDL		-	
		58	ALETSVHEI		-	
PV18.E6.47	EN EUR STEEL					
EVIO.E6.4/	FAFKDLFVV	16	FAFRDLCIV		_	
		18	FAFKDLFVV		+	350.6
		31	FAFTDLTIV		-	
		33	FAFADLTVV		_	31.4
		45	FAFKDLCIV		-	176.9
		52	FLFTDLRIV		-	
		56	FACTELKLV			
	·	58	FVFADLRIV		_	7.7

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HPV31.E6.45	FAFTDLTIV	16	FAFRDLCIV	·	
		18	FAFKDLFVV		
"		31	FAFTDLTIV		
		33	FAFADLTVV	+	20.7
		45	FAFKDLCIV	+	11.6
		52	FLFTDLRIV		
		56	FACTELKLV		
		58	FVFADLRIV	-	
			TVIIDBRIV	-	
HPV52.E6.45	FLFTDLRIV	16	FAFRDLCIV		
		18.	FAFKDLFVV		
•		31	FAFTDLTIV	-	
		33	FAFADLTVV	-	
		45	FAFKDLCIV		
		52	FLFTDLRIV		
	·	56	FACTELKLV	+	421.4
		58	FVFADLRIV		57.5
			TVITADDRIV	+	94.1
HPV58.E6.45	FVFADLRIV	16	FAFRDLCIV		
		18	FAFKDLFVV	-	
		31	FAFTDLTIV		
		33	FAFADLTVV		
		45	FAFKDLÇIV		
		52	FLFTDLRIV		122
		56	FACTELKLV		13.3
		58	FVFADLRIV		21.0
			IVIADDRIV	+ '	62.8
HPV18.E7.7	TLQDIVLHL	16	TLHEYMLDL		<u> </u>
		18	TLQDIVLHL		
		31	TLQDYVLDL	+ :	99.0
		33	TLKEYVLDL		
****		45	TLQEIVLHL		ļ
		52	TIKDYILDL		
		56	TLQDVVLEL	_	
		58	TLREYILDL	+	38.0
			TRICETTEDE		
HPV16.E7.82	LLMGTLGIV	16	LLMGTLGIV		
		18	LFLNTLSFV	The second secon	518.5
		31	LLMGSFGIV		
		33		+	90.1
		45	LLMGTVNIV LFLSTLSFV		
		52	MLLGTLQVV	+	
		56		-	
		58	LLMGALTVT LLMGTCTIV	+	
		- 30	TILMGICITY		
HPV33.E7.81	LLMGTVNIV	16	I I MOTT CITY		
		18	LLMGTLGIV LFLNTLSFV		
		31		-	
		33	LLMGSFGIV		ļ
		45	LLMGTVNIV	+	179.4
			LFLSTLSFV		
		52	MLLGTLQVV	+	
		56	LLMGALTVT	_	20.8
		58	LLMGTCTIV		

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HPV52.E7.84	MLLGTLQVV	. 16	LLMGTLGIV		
		18	LFLNTLSFV		
		31	LLMGSFGIV		
		33	LLMGTVNIV	+	
		45	LFLSTLSFV		
		52	MLLGTLQVV	+	99.8
		56	LLMGALTVT		
		58	LLMGTCTIV	_	
17715 6 77 00					
HPV56.E7.89	LLMGALTVT	16	LLMGTLGIV		7
		18	LFLNTLSFV	-	
		31	LLMGSFGIV		
		33	LLMGTVNIV	+	
		45	LFLSTLSFV	_	
		52	MLLGTLQVV	-	
		56	LLMGALTVT	+	263.5
		58	LLMGTCTIV	_	43.6
					

Table 10. 167 HIV-1 Variants

SEQ	Sequence	Name	Accession	Cult	
ID NO	Designation	Name	Number	SubType	Country
	JG.92UG037 U51190	92UG037	U51190	Α	UG
	Y.97BL006 AF1932	97BL006	AF193275	Ä	BY
	E.Q23 AF004885	Q23	AF004885	Â	KE
	SE.SE6594 AF06967	SE6594	AF069672	Â	SE
	E.SE7253 AF06967	SE7253	AF069670	Â	SE
	E.SE7535_AF06967	SE7535	AF069671	Â	SE
	E.SE8538 AF06966	SE8538	AF069669	Â	SE
A.S	E.SE8891 AF06967	SE8891	AF069673	Â	SE
A.U	JG.U455_M62320	U455	M62320	Â	UG
A.S	E.UGSE8131_AF107	UGSE8131	AF107771	A	SE
A2.	CY.94CY017.41_AF	94CY017.41	AF286237	A2	CY
A2.	CD.97CDKTB48_AF2	97CDKTB48	AF286238	A2	CD
	D97KR004_AF286	97KR004	AF286239	A2D	KR
A20	G.CD.97CDKP58_AF3	97CDKP58	AF316544	A2G	CD
AC.	.IN.21301_AF06715	21301	AF067156	AC	IN
AC.	.RW.92RW009_U8882	92RW009	U88823	AC	RW
	SE.SE9488_AF0714	SE9488	AF071474	AC	SE
	D.SE.SE8603_AF075	SE8603	AF075702	ACD	SE
	G.BE.VI1035_AJ276	VI1035	AJ276595	ACG	BE
	SE.SE6954_AF0757	SE6954	AF075701	AD	SE
	SE.SE7108_AF0714	SE7108	AF071473	AD	SE
	HK.NO.97NOGIL3_AJ	97NOGIL3	AJ237565	ADHK	NO
ADł	K.CD.MAL_X04415	MAL	X04415	ADK	CD
	.NG.92NG003_U8882	92NG003	U88825	AG	NG
	BE.VI1197_AJ2765	Vi1197	AJ276596	AG	BE
	HU.GA.VI354_AF076	VI354	AF076474	AGHU	GA
	U.CD.Z321_U76035	Z321	U76035	AGU	CD
	BW.BW2117_AF1921	BW2117	AF192135	AJ	BW
	L.3202A21_U34604	3202A21	U34604	В	NL
	S.BC_L02317	BC	L02317	В	US
	B.CAM1_D10112	CAM1	D10112	В	GB
	E.D31_U43096	D31	U43096	В	DE
	S.DH123_AF069140	DH123	AF069140	В	US
	B.GB8.C1_Y13716	GB8	AJ271445	В	·GB
	E.HAN_U43141	HAN	U43141	В	DE
	R.HXB2_K03455	HXB2	K03455	В	FR
	S.JRCSF_M38429	JRCSF	M38429	В	US
B.G	B.MANC_U23487	MANC	U23487	В	GB
	S.MNCG_M17449	MNCG	M17449	В	US
	A.OYI,_M26727	OYI	M26727	В	GA
	S.P896_U39362	P896	M96155	В	US
	S.RF_M17451	RF	M17451	В	US
B.C.	N.RL42_U71182	RL42	U71182	В	CN
	S.SF2_K02007	SF2	K02007	В	บร
D. I \	W.TWCYS_AF086817	TWCYS	AF086817	В	TW
D.AU	U.VH_AF146728	VH	AF146728	В	AU
	S.WEAU160_U21135 R.WK_AF224507	WEAU160	U21135	В	US
D.NI	1VIN_AF4243U/	WK	AF224507	В	KR

B.US.WR27_U26546	WR27	U26546	В	1.10
B.US.YU2 M93258	YU2	M93258	B B	US
BF1.BR.93BR029.4 AF	93BR029.4	AF005495	BF1	US
C.BR.92BR025_U52953	92BR025	U52953		BR
C.IN.93IN101_AB0238	93IN101	AB023804	C	BR
C.IN.93IN904_AF0671	93IN904	AF067157	C	IN
C.IN.93IN999_AF0671	93IN999	AF067154		IN
C.IN.94IN11246 AF06	94IN11246	AF067159	C	IN
C.IN.95IN21068 AF06	95IN21068		C	IN
C.BW.96BW0402 AF110	96BW0402	AF067155	C	IN
C.BW.96BW1210 AF110	96BW1210	AF110962	C	BW
C.BW.96BW15B03_AF11	96BW15B03	AF110972	C	BW
C.ET.ETH2220_U46016	ETH2220	AF110973	C	BW
C.BW.96BW11B01 AF11		U46016	C	ET
C.BW.00BW0762.1_AF44	96BW11	AF110969	Ċ	BW
C.BW.00BW0768.20_AF44	00BW0762.1	AF443088	C	BW
C.BW.00BW0874.21 AF44	00BW0768.20	AF443089	С	BW
C.BW.00BW1471.27_AF44	00BW0874.21	AF443090	С	BW
C.DW.00DW1471.27_AF44	00BW1471.27	AF443091	C	BW
C.BW.00BW1616.2_AF44	00BW1616.2	AF443092	C	BW
C.BW.00BW1686.8_AF44	00BW1686.8	AF443093	. C	BW
C.BW.00BW1759.3_AF44	00BW1759.3	AF443094	C	BW
C.BW.00BW1773.2_AF44	00BW1773.2	AF443095	С	BW
C.BW.00BW1783.5_AF44	00BW1783.5	AF443096	С	BW
C.BW.00BW1795.6_AF44	00BW1795.6	AF443097	С	BW
C.BW.00BW1811.3_AF44	00BW1811.3	AF443098	С	BW
C.BW.00BW1859.5_AF44	00BW1859.5	AF443099	С	BW
C.BW.00BW1880.2_AF44	00BW1880.2	AF443100	С	BW
C.BW.00BW1921.13_AF44	00BW1921.13	AF443101	C	BW
C.BW.00BW2036.1_AF44	00BW2036.1	AF443102	C	BW
C.BW.00BW2063.6_AF44	00BW2063.6	AF443103	Ċ.	BW
C.BW.00BW2087.2_AF44	00BW2087.2	AF443104	C	BW
C.BW.00BW2127.214_AF44	00BW2127.214	AF443105	Č	BW
C.BW.00BW2128.3_AF44	00BW2128.3	AF443106	Č	BW
C.BW.00BW2276.7_AF44	00BW2276.7	AF443107	č	BW
C.BW.00BW3819.3_AF44	· 00BW3819.3	AF443108	Č	BW
C.BW.00BW3842.8_AF44	00BW3842.8	AF443109	Č	BW
C.BW.00BW3871.3_AF44	00BW3871.3	AF443110	č	BW
C.BW.00BW3876.9_AF44	00BW3876.9	AF443111	Č	BW
C.BW.00BW3886.8_AF44	00BW3886.8	AF443112	č	BW
C.BW.00BW3891.6_AF44	00BW3891.6	AF443113	č	BW
C.BW.00BW3970.2_AF44	00BW3970.2	AF443114	č	BW
C.BW.00BW5031.1_AF44	00BW5031.1	AF443115	Č	BW
C.BW.96BW01B21_AF11	96BW01B21	AF110960	. C	
C.BW.96BW0407 AF11	96BW0407	AF110963	C	BW
C.BW.96BW0502_AF11	96BW0502	AF110967	C	BW
C.BW.96BW06.J4 AF29	96BW06.J4	AF290028	C	BW
C.BW.96BW11.06_AF11	96BW11.06	AF110970	C	BW
C.BW.96BW1210_AF11	96BW1210			BW
C.BW.96BW15B03_AF11		AF110972	C	BW
C.BW.96BW16.26_AF11	96BW15B03 96BW16.26	AF110973	C	BW
C.BW.96BW17A09_AF11		AF110978	C	BW
C.BW.96BWMO1.5 AF44	96BW17A09	AF110979	C	BW
C.BW.96BWMO3.2 AF44	96BWMO1.5	AF443074	C	BW
C.BW.98BWMC12.2_AF44	96BWMO3.2	AF443075	C	BW
5.511.50511NC12.2_AF44	98BWMC12.2	AF443076	С	BW

C.BW.98BWMC13.4 AF44	98BWMC13.4	AF443077	С	DW
C.BW.98BWMC14.a3 AF44	98BWMC14.a3	AF443078	Č	BW
C.BW.98BWMO14.10 AF44	98BWMO14.10	AF443079	č	BW
C.BW.98BWMO18.d5 AF44	98BWMO18.d5	AF443080	Č	BW
C.BW.98BWMO36.a5 AF44	98BWMO36.a5	AF443081	č	BW
C.BW.98BWMO37.d5 AF44	98BWMO37.d5	AF443082	Č	BW
C.BW.99BW3932.12 AF44	99BW3932.12	AF443083		BW
C.BW.99BW4642.4_AF44	99BW4642.4	AF443084	C	BW
C.BW.99BW4745.8 AF44	99BW4745.8		C	BW
C.BW.99BW4754.7 AF44	99BW4754.7	AF443085	C	BW
C.BW.99BWMC16.8_AF44		AF443086	C	BW
CRF01_AE.CF.90CF11697	99BWMC16.8	AF443087	C	BW
CRF01_AE.CF.90CF402_U5	90CF11697	AF197340	CRF01_AE	CF
CRF01_AE.CF.90CF402_05	90CF402	U51188	CRF01_AE	CF
CRF01_AE.TH.93TH057_AF	90CF4071	AF197341	CRF01_AE	CF
CDE01 AS TH 03TH057_AF	93TH057	AF197338	CRF01_AE	TH
CRF01_AE.TH.93TH065_AF	93TH065	AF197339	CRF01_AE	TH
CRF01_AE.TH.93TH253_U5	93TH253	U51189	CRF01_AE	TH
CRF01_AE.TH.95TNIH047	95TNIH047	AB032741	CRF01_AE	TH
CRF01_AE.TH.CM240_U547	CM240	U54771	CRF01_AE	TH
CRF01_AE.TH.TH022_AB03	TH022	AB032740	CRF01_AE	TH
CRF02_AG.SN.98SEMP1211	98SEMP1211	AJ251056	CRF02_AG	SN
CRF02_AG.FR.DJ263_AF06	DJ263	AF063223	CRF02_AG	FR
CRF02_AG.FR.DJ264_AF06	DJ264	AF063224	CRF02_AG	FR
CRF02_AG.GH.G829_AF184	G829	AF184155	CRF02 AG	GH
CRF02_AG.NG.IBNG_L3910	IBNG	L39106	CRF02 AG	NG
CRF02_AG.SE.SE7812_AF1	SE7812	AF107770	CRF02 AG	SE
CRF03_AB.RU.KAL153-2_A	KAL153-2	AF193276	CRF03_AB	RU
CRF03_AB.RU.RU98001_AF	RU98001	AF193277	CRF03_AB	RU
CRF04_cpx.CY.94CY032-3	94CY032-3	AF049337	CRF04 cpx	CY
CRF04_cpx.GR.97PVCH_AF	97PVCH	AF119820	CRF04 cpx	GR
CRF04_cpx.GR.97PVMY_AF	97PVMY	AF119819	CRF04 cpx	GR
CRF05_DF.BE.VI1310_AF1	VI1310	AF193253	CRF05 DF	BE
CRF05_DF.BE.VI961_AF07	VI961	AF076998	CRF05 DF	BE
CRF06_cpx.ML.95ML127 A	95ML127	AJ288982	CRF06_cpx	ML
CRF06_cpx.ML.95ML84 AJ	95ML84	AJ245481	CRF06_cpx	
CRF06_cpx.SN.97SE1078	97SE1078	AJ288981	CRF06_cpx	ML
CRF06_cpx.AU.BFP90_AF0	BFP90	AF064699	CRF06_cpx	SN
CRF11_cpx.CM.97CM-MP81	97CM-MP818	AJ291718	CRF00_cpx	AU
CRF11_cpx.GR.GR17_AF17	GR17	AF179368		CM
D.CD.84ZR085 U88822	84ZR085	U88822	CRF11_cpx	GR
D.UG.94UG1141 U8882	94UG1141		D	CD
D.CD.ELI_K03454	ELI	U88824	D	UG
D.CD.NDK_M27323		K03454	D	CD
F1.BR.93BR020.1 AF0	NDK	M27323	D	.CD
F1.FI.FIN9363_AF075	93BR020.1	AF005494	F1	BR
F1.FR.MP411_AJ24923	FIN9363	AF075703	F1	FI
E1 DE 1/19E0 AF07722	MP411	AJ249238	F1	FR
F1.BE.VI850_AF07733	VI850	AF077336	F1	BE
F2.CM.MP257_AJ24923	MP257	AJ249237	F2	CM
F2KU.BE.VI1126_AF07	VI1126	AF076475	F2KU	BE
G.NG.92NG083_U88826	92NG083	U88826	G	NG
G.BE.DRCBL_AF084936	DRCBL	AF084936	G	BE
G.SE.SE6165_AF06164	SE6165	AF061642	G	SE
H.CF.90CF056_AF0054	90CF056	AF005496	н	CF
H.BE.VI991_AF190127	VI991	AF190127	Н	BĘ
				-

60458026 032803

H.BE.VI997_AF190128	VI997	AF190128	н	BE
J.SE.SE7022_AF08239	SE7022	AF082395	j	SE
J.SE.SE7887_AF08239	SE7887	AF082394	Ĵ	SE
K.CD.EQTB11C_AJ2492	EQTB11C	AJ249235	ĸ	CD
K.CM.MP535_AJ249239	MP535	AJ249239	ĸ	CM
N.CM.YBF30_AJ006022	YBF30	AJ006022	Ñ	CM
O.SN.99SE-MP1299_ZX	SEMP1299	AJ302646	Ö	SN
O.SN.99SE-MP1300_ZX	SEMP1300	AJ302647	Ö	SN
O.CM.ANT70_L20587	ANT70	L20587	Ö	CM
O.CM.MVP5180_L20571	MVP5180	L20571	O	CM
U.CD83CD0031	83CD0031	AF286236	Ú	CD

Table 11. HIV Gag Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

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Name: 00BW0762 1
                         Len:
                                 556
                                      Check: 2513
                                                    Weight:
                                                              1.00
Name: 00BW0768 2
                         Len:
                                 556
                                      Check: 8965
                                                    Weight:
                                                              1.00
Name: 00BW0874 2
                         Len:
                                 556
                                      Check: 9574
                                                    Weight:
                                                              1.00
Name: 00BW1471_2
                         Len:
                                 556
                                      Check: 5395
                                                    Weight:
                                                              1.00
Name: 00BW1616 2
                         Len:
                                 556
                                      Check: 4692
                                                    Weight:
                                                              1.00
Name: 00BW1686 8
                                556
                         Len:
                                      Check: 7822
                                                    Weight:
                                                              1.00
Name: 00BW1759 3
                         Len:
                                556
                                      Check: 7777
                                                    Weight:
                                                              1.00
Name: 00BW1773_
                                      Check: 9727
                         Len:
                                556
                                                    Weight:
                                                              1.00
Name: 00BW1783_5
                         Len:
                                      Check: 9681
                                556
                                                    Weight:
                                                              1.00
Name: 00BW1795 6
                         Len:
                                556
                                      Check: 9667
                                                    Weight:
                                                              1.00
Name: 00BW1811 3
                         Len:
                                556
                                      Check: 4422
                                                    Weight:
                                                              1.00
Name: 00BW1859 5
                         Len:
                                556
                                      Check: 7320
                                                    Weight:
                                                              1.00
Name: 00BW1880 2
                         Len:
                                556
                                      Check: 1603
                                                    Weight:
                                                              1.00
Name: 00BW1921_1
                         Len:
                                556
                                      Check: 883
                                                  Weight:
                                                             1.00
Name: 00BW2036_1
                         Len:
                                556
                                      Check: 2591
                                                    Weight:
                                                              1.00
Name: 00BW2063_6
                         Len:
                                556
                                      Check: 5152
                                                   Weight:
                                                              1.00
Name: 00BW2087 2
                         Len:
                                556
                                      Check: 5183
                                                    Weight:
                                                              1.00
Name: 00BW2127 2
                                     Check: 5469
                         Len:
                                556
                                                   Weight:
                                                              1.00
Name: 00BW2128 3
                         Len:
                                556
                                      Check: 9621
                                                   Weight:
                                                              1.00
Name: 00BW2276 7
                                      Check: 4153
                         Len:
                                556
                                                   Weight:
                                                              1.00
Name: 00BW3819 3
                         Len:
                                556
                                      Check: 4227
                                                   Weight:
                                                              1.00
Name: 00BW3842 8
                         Len:
                                556
                                     Check: 9312
                                                   Weight:
                                                              1.00
Name: 00BW3871 3
                                     Check: 501
                         Len:
                                556
                                                  Weight:
                                                             1.00
Name: 00BW3876_9
                                     Check: 773
                         Len:
                                556
                                                  Weight:
                                                             1.00
Name: 00BW3886 8
                         Len:
                                     Check: 2351 Weight:
                                556
                                                              1.00
Name: 00BW3891 6
                         Len:
                                556
                                      Check: 129
                                                  Weight:
                                                             1.00
Name: 00BW3970 2
                         Len:
                                556
                                     Check: 8768
                                                   Weight:
                                                              1.00
Name: 00BW5031 1
                         Len:
                                556
                                     Check: 3966
                                                   Weight:
                                                              1.00
Name: 96BW01B21
                                     Check: 602
                         Len:
                                556
                                                  Weight:
                                                             1.00
Name: 96BW0407
                        Len:
                                556
                                     Check: 9836
                                                   Weight:
                                                              1.00
Name: 96BW0502
                        Len:
                                556
                                     Check: 6402
                                                   Weight:
                                                              1.00
Name: 96BW06 J4
                        Len:
                                556
                                     Check: 254
                                                  Weight:
                                                             1.00
Name: 96BW11 06
                        Len:
                                556
                                     Check: 6801
                                                   Weight:
                                                              1.00
Name: 96BW1210
                        Len:
                                556
                                     Check: 6016
                                                   Weight:
                                                              1.00
Name: 96BW15B03
                        Len:
                                556
                                     Check: 6072
                                                   Weight:
                                                              1.00
Name: 96BW16 26
                        Len:
                                556
                                     Check: 9409
                                                   Weight:
                                                              1.00
Name: 96BW17A09
                        Len:
                                556
                                     Check: 2723
                                                   Weight:
                                                              1.00
Name: 96BWMO1 5
                        Len:
                                556
                                     Check: 5051
                                                   Weight:
                                                              1.00
Name: 96BWMO3_2
                        Len:
                                556
                                     Check: 496
                                                  Weight:
                                                             1.00
Name: 98BWMC12 2
                        Len:
                                556
                                     Check: 1164 Weight:
                                                              1.00
Name: 98BWMC13 4
                        Len:
                                556
                                     Check: 4961
                                                   Weight:
                                                              1.00
Name: 98BWMC14 a
                        Len:
                                556
                                     Check: 7351
                                                   Weight:
                                                              1.00
Name: 98BWM014 1
                        Len:
                                     Check: 288 Weight:
                                556
                                                             1.00
Name: 98BWMO18 d
                        Len:
                                556
                                     Check: 6836
                                                  Weight:
                                                              1.00
Name: 98BWM036_a
                        Len:
                                556
                                     Check: 4386
                                                   Weight:
                                                              1.00
Name: 98BWM037_d
                                     Check: 6900
                        Len:
                                556
                                                   Weight:
                                                              1.00
Name: 99BW3932_1
                        Len:
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A_SE_SE889
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A SE UGSE8
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 AC SE SE94
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 ACD SE SE8
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            ... RASVLSG .GKLDAWEKI RLRPGGRKKY KLKHIVWASR ELERFALNPS
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B_GA_OYI__
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B_KR_WK_AF
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B US BC LO
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B US DH123
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ACD_SE SE8
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          RQANFLGKIW PSNKG.RPGN FPQSRPEPTA PP....AEP TAPPAESFG.
ACG BE VII
          RQANFLGKIW PSSKG.RPGN FLQSRP.... EP TAPPAESFG.
AD SE SE69
          ......
AD_SE SE71
ADHK NO 97
          RQANFLGKIW PSSKG.RPGN FPQSRPE... ......PS APPA.ESFG.
ADK CD MAL
          RQANFLGKIW PSHKG.RPGN FLQSRPB... ......PT APPA.ESFG.
AG_BE_VI11
          RQANFLGKIW PSSKG.RPGN FPQSRLE... .....PT APPA.ESLG.
          RQANFLGKIW PSNKG.RPGN FLQNRPE... ..... P TAPPAESFG.
AG NG 92NG
          RQANFLGKIW PSNKG.RPGN FLQNRPE......PT APPA.ESFG.
AGHU GA VI
          RQANFLGKIW PSNKG.RPGN FLQNRPE... ..... P TAPPAESFE.
AGU_CD Z32
          RQANFLGKIW PSNKG.RPGN FLQSRPE........PT APPA.ESFG.
AJ BW BW21
B AU VH AF
          RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPEESFR.
          RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPEESFR.
B CN RL42
          RQANFLGKIW PSYKG.RPGN FLQRRPE...... P TAPPEESFR.
B DE D31 U
          RQANFLGKIW PSHKG.RPGN FLOSRPE... ...... TAPPEESFR.
B DE HAN U
          RQANFLGKIW PSYKG.RPGN FLQSRPE... ..... P TAPPEESFR.
B_FR_HXB2_
B_GB_CAM1_
          RQANFLGKIW PSHKG.RPGN FLQNRPE...... TAPPAESFG.
          RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPEESFR.
          RQANFLGKIW PSHKG.RPGN FLQSRPEPIA PP.....EP TAPPEESFR.
B GB GB8 A
B GB MANC_
          RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPEESFR.
B_KR_WK_AF RQANFLGKIW PSHKG.RPGN FLQSRPE...... P SAPPEESFR.
         RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... TAPPEESFR.
B NL 3202A
          RQANFLGKIW PSHKE.RPGN FLQSRPE...... P TAPPEESFR.
B TW TWCYS
         RQANFLGKIW PSHKG.RPGN FPQSRLE....P TAPPEESFR.
B US BC LO
          RQANFLGKIW PSHKE.RPGN FLQSRPE... .....P SAPPEESFR.
B_US_DH123
B_US_JRCSF RQANFLGKIW PSYKG.RPGN FLQSRPE... ..... P TAPPEESFR.
B_US_MNCG_ RQANFLGKIW PSCKG.R.RN FPQSRTE... ..... P TAPPEESFR.
B_US_P896_
          RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPEESFR.
B_US_RF_M1 RQANFLGKIW PSHKG.RPGN FLQSRPE...... P TAPPEESFR.
B_US_SF2_K
         RQANFLGKIW PSYKG.RPGN FLQSRPE...... P TAPPEESPR.
          RQANFLGKIW SSQKG.RPGN FPQSRLE... ..... P TAPPEESFR.
B US WEAU1
B US WR27
          RQAXFLGXIR PSHXG.RPGX FLQNRPE...... P SAPPAESFR.
         RQANFLGKIW PSHKG.RPGN FLQSRPE.....P TAPSEESVR.
B US YU2 M
         RQANFLGKIW PSHKG.RPGN FLQSRPE.....P TAPPAESFR.
BF1_BR 93B
          RQANFLGKIW PSHRG.RPGN LLQNRT.....EP TAPPE.....
C BR 92BR0
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RQANFLGKIW PSHKG.RPGN FLQ......SRPEP TAPPAESFR.
C_BW 96BW0
           RRANFLGKIW PSHKG.RPGN FLQSRPE...... TAPPAESF..
C BW 96BW1
           GQANFLGKIW PSHKG.RPGN FLQSR..... PEP SAPPAESFR.
C BW 96BW1
C BW 96BW1
           RQANFLGKIW PSHKG.RPGN FLQNRTEP...... TAPPAESFK.
           RQANFLGRLW PSNKG.RPGN FLQSRP.... EP TAPPESLRPE
C ET ETH22
C_IN_93IN1 RQANFLGKIW PSHKG.RPGN FLQ......SRPEP TAPPAESFR.
C_IN_93IN9 RQANFLGKIW PSHKG.RPGN FLQ...... SRPEP TAPPAESFR.
C_IN_93IN9 RQANFLGKIW PSHKG.RPGN FLQNRPEPTA PP...ARPEP TAPPAESFR.
C_IN_94IN1 RQANFLGKIW PSHKG.RPGN FLQ...... SRPEP TAPPAESFR.
C_IN_95IN2
           RQANFLGKIW PSHKG.RPGN FLQ...... SRPEP TAPPAESFR.
CRF01 AE C
           RQANFLGKIW PLNKG.RPGN FPQSRLE... .....PT APPA.ESLG.
           RQANFLCKIW PSSKC.RPGN FPQSRPE.....PT APPM.ESLG.
CRF01 AE C
CRF01 AE C
           RQANFLGRIW PSSKG.RPGN FPQSRPE... .....PT APPA.ESLG.
CRF01 AE T
           RQANFLGKFW PSNKG.RPGN FPQSRPE... .....PT APPA.ENWG.
           RQANFLGKIW PSNKG.RPGN FPQSRPE... .....PT APP..ABWG.
CRF01 AE T
           RQANFLGKIW PSNKG.RPGN FPQSKPE... ..... PT APPA.ENWG.
CRF01 AE T
           RQANFLGKIW PSNKG RPGN FPQSRPE... ... PT APPA ENWG.
CRF01 AE T
           RQANFLGKIW PSNKG.RPGN FPQSRPE... ......PT APPA.ENWG.
CRF01_AE_T
           RQANFLGKIW PSNKG.RPGN FPQSRPE... .....PT APPA.ENWG.
CRF01_AE_T
           GQANFLGKIW PSSKG.RPGN FPQSRPE... ......PT APPA.ESLG.
CRF02_AG_F
CRF02_AG_F
           RQANFLGKIW PSSKG.RPGN FPQSRPE... .....PT APPA.BSFG.
           RQANFLGKIW PSNKG.RPGN FPQSRPE... P..... SAPPAESFG.
CRF02 AG G
CRF02 AG N
           RQANFLGKIW PSSKG.RPGN FPQSRPE... .....PT APPA.ESFG.
CRF02_AG S
           RQANFLGKIW PSSKG.RPGN FPQSRPE... .....PT APPA.ESLG.
CRF02 AG S
           RQANFLGKIW PSSKG.RPGN FPQSRPE... .....PT APPA.ESFG.
           RQANFLGRIW PSSKG.RPGN FPQSRPE.........PS APP.AENFG.
CRF03 AB R
CRF03_AB_R RQANFLGKIW PSSKG.RPGN FPQSRPE........PS APP.AENFG.
           RQANFLGRMW PSSKG.RPGN FLQNRPE... .....PT APPA.ECLE.
CRF04_cpx_
           RQANFLGRMW PSSKG.RPGN FLQSRPE... .....PT APPA.ESLE.
CRF04_cpx_
           RQANSLGRMW PSSKG.RPGN FLQSRTE... .....PT APPA.ESFE.
CRF04_cpx_
           RQANFLGKVW PSHKG.RPGN FLQSRP.... EP SAPPAESFR.
CRF05_DF_B
CRF05_DF_B GQANFLGRVW LSHKG.RPGN FLQSRP.... EP SAPPAESFG.
CRF06_cpx_
           RQANFLGKIW PSNKG.RPGN FLQNRPE... ..... P TAPPIESFG.
CRF06_cpx_
           RQANFLGKIW PSNKG.RPGN FLQNRPE... ..... TAPPABSFG.
CRF06_cpx_
           RQANFLGRIW PSSKG.RPGN FLQNRPE... ..... P TAPPAESFG.
CRF06_cpx_
           ROANFLGKIW PSHKG.RPGN FLONRPEONR P.....EP SAPPAESFG.
           RQANFLGKIW PSSKG.RPGN FLQSRPE... ......PT APPA.ESFG.
CRF11_cpx_
           RQANFLGKIW PSSKG.RPGN PLQSRPE... ...... PT APPA.ESFG.
CRF11 cpx
           RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPAE.FG.
D CD 84ZRO
           RQANFLGRIW PSHKG.RPGN FLQSRP... EP TAPPAESFG. RQANFLGKIW PSHKG.RPGN FLQSRP... EP TAPPAESFG.
D CD ELI K
D_CD_NDK_M
           RQANFLGKIW PSHNG.RPGN FLQSRPPA.....EP TAPPAEIFG.
D_UG_94UG1
           RQANFLGKIW PSNKG.RPGN FLQSRPE... ..... P TAPPAESFG.
F1_BE_VI85
           RQANFLGKIW PSNKG.RPGN FIQNRPE... ..... P SAPPAESFR.
F1 BR 93BR
F1 FI FIN9
           RQANFLGKIW PSNKG.RPGN FLQSRPE....... P TAPPAESLG.
F1 FR MP41
           RQANFLGKIW PSNKG.RPGN FLQNRPE... ..... TAPPAESFG.
           RQANFLGKMW PSNKG.RPGN FLQNRPE... ..... TAPPAESFG.
F2 CM MP25
           RQANFLGKIW PSNKG.RPGN FLQSRPE... ..... TAPPAESFG.
F2KU BE VI
           RQANFLGKIW PSNKG.RPGN FLQNRPE....P TAPPAENFG.
G BE DRCBL
           RQANFLGKIW PSNKG.RPGN FLQNRTE... P TAPPAESFG.
G_NG_92NG0
G_SE_SE616
           RQANFLGKIW PSNKG.RPGN FLQNRTE... P TAPPAESLG.
H_BE_VI991
           RQANFLGKIW PSSKG.RPGN FPQKRLE... ..... TAPPAESFG.
H_BE_VI997
H_CF_90CF0
           RQANFLGKIW PSSKG.RPGN FLQSRPE... ..... P TAPPAESFG.
           RQANFLGKIW PSSKG.RPGN FLQSRPE... .....P TAPPAESFG.
J SE SE702
           RQANFLGKIW PSSKG.RPGN FLQSRPE... ...... P TAPPAESLG.
J SE SE788
           RQANFLGKIW PSSKG.RPGN FLQSRPE... ...... P TAPPAESLG.
K CD EQTB1
           RQANFLGKFW PLNKE.RPGN FLQNRPE... ..... P TAPPAESFG.
K CM MP535
           RQANFLGKIW PSHKG.RPGN FLQSRPE... ..... P TAPPAESFG.
N CM YBF30
           RQANFLGKSW SPFKG.RPGN FPQTTTRK.. .....EP TAPPLESYG.
O_CM_ANT70
           KQANFLGKYW PP.GGTRPGN YVQRPAH... P SAPPMEEEVK
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O CM MVP51	DONNEL CRAM	DD COMPRA			
O SN 99SE	MANUL DON'I M	PP.GGTRPGN	YVQKQVS		SAPPMEEAVK
0_SN_99SE_	KOVNETCKAM	PP.GGTRPGN	YAQRQVS	P	SAPPMTEEMK
U_CD83C	PODNETCKIM	DENIES DOON	YAQRQVS	P	SAPPMTEEMK
0_ CD03C	WOMEN DOLLIN	PSNAG. RPGN	FLQNRPE	P	TAPPAESFG.
	501				550
00BW0762_1	FE	ETNPTP	KOE.	PKDRE	DI.TSI KSI BO
00BW0768_2	FE	.ETTTPAP	KOE	LKDRE	PLTALKSLEG
00BW0874_2	FE	ETTPAL	KRE	LKERE	PLISLKSLEG
00BW1471_2	FE	ETTPAP	KQE	PKDRE	PLTSLKSLFG
00BW1616_2	F	.GETTPSP	RQE	AKDRE	PLISLKSLEG
00BW1686_8	PE		KQE	PKDRE	PLTSLKSLFG
00BW1759_3	FE		KQE	PKDRE	TLTSLRSLFG
00BW1773_2	FE	ETTPAP	KQB	PKDRE	PLTSLKSLFG
00BW1783_5	FB		KQB	TKDRE	PLTSLKSLFG
00BW1795_6	P	.EETTPSP	KQB	LKDKE	PLTSLKSLFG
00BW1811_3	FE	ETTPAS	KQE	KKDRE	TLTSLRSLFG
00BW1859_5	FE	ETTPAP	KQE	QKDRE	PLTSĻKSLFG
00BW1880_2 00BW1921 1	PD	ETTPAP	KQE	PKDRE	PLTSLKSLFG
00BW1921_1	rs	ETTPAP	KQE	PKDRE	PLTSLKSLFG
00BW2033_1	££	EETTPAP	KQE	LKDRE	PLISLKSLFG
00BW2087 2	PP	ETTPAS	KQE	MKDKE	PLISLKSLLG
00BW2127 2	PR	ETTHAP		LKDRE	PLTSLKSLFG
00BW2128 3	FE	ETTPAP	VQE	LKDRE	ALTSLKSLFG
00BW2276 7	FE	ETTPEL	KOG	PKNREE	PLTSLKSLFG
00BW3819 3	FE	EITPAP	KOE	TKDRE	PLTSLKSLFG
00BW3842 8	FE	ETTPAP	KOE	PKDRGPY.RE	PLISLKSLEG
00BW3871 3	FE,	ETTPVP		PTDRE	DITCLECIEC
00BW3876 <u></u> 9	FE	ETTPTL		LKDRE	DITCINCI DO
00BW3886_8	FE	ETTPVP		QKDRE	ALTSLKSLEG
00BW3891_6	FE		KQE	PKDRE	PLTSLKSLEG
00BW3970 <u>2</u>	FE		KOE	PKDRE	PLISLKSLEG
00BW5031_1	FG	ETTPAP	KOE	MKERE	PLISLKSLFG
96BW01B21	FE	ETTPAP	KOE	PKDRE.	DI.TGI.DGI.EC
96BW0407	FE	ETTPGQ	KQE	SKDRE	TLTSLKSLFG
96BW0502	FE	ETTPAP	KOE	PKDREPY RE	DI.TAI.DSI.EG
96BW06_J4	FE	ETTPAL	KQE	PKDKE	PLTSLKSPFG
96BW11_06		EETTPAP	KOE	TKDRE.	PLTSLKSLEG
96BW1210 96BW15B03	FE	ETTPAQ	KQE	PKDREP	PLASLKSLFG
96BW16 26	FE	ETTPAP	KQE	PKDRE	PLISLKSLFG
96BW17A09	FG	ETTPAP	KQE	PKDRE	PLTSLRSLFG
96BWM01 5		EETTPAP	KQE	PKDRE	PLTSFKSLFG
96BWM03_2	PE	DTADDAE	RQE	MKDKEPY.KE SKDRE	PLISLRSLFG
	LE	ETTDAC	KOE	SKDRE	PLISLKSLFG
98BWMC13 4		EETTPAD	KOE	PKDKE	PLISTKSLFG
98BWMC14 a	FE	. ETTPAP	KOE	QKDRE	PLUCIKSTEG
98BWM014 1		EPTAPPAES.	FROE	PKDRE	DITALKSLEG
98BWM018 d	FE	ETTPAL	KOE	PKDREA	PLIADASLEG
98BWM036_a	FE	ETNLAP	KOE	PKDRE	DITTELKELEC
98BWM037_d	FE	ETTPAP	ROE	AKDKE	PLNSI-KSI-FC
99BW3932 <u>1</u>	FE	ETTPAP	KQE	LKDRE	ALTSLKSLFC
99BW4642_4	FE	ETTPAP	KQE	PKDRE	PLTSLKSLFG
99BW4745_8	FE	GATPTP	KQE	PRDRE	PLTSLKSLFG
99BW4754_7	· · · · · · FE · · ·	ETTPTQ	KQE	SKDRE	PLTSLKSLFG
99BWMC16_8	FE	ETNPAP	KQE	LKNRE	TLTSLRSLFG
A2_CD_97CD	• • • • • • • • • •	\dots EEITSSL	KQE	NREPST	PAISLKSLFG
A2_CY_94CY	• • • • • • • • • • •	.MGEEITSSL	KQELE	TREPYN	PAISLKSLFG
A2D97KR	•••••	.MGEETTPLQ	KQELK	NREQHT	PAISLKSLFG

A2G_CD_97C		MODELE			
A_BY_97BL0		MGEEIT	PSLK.O. R	OKDRE OVD	Deter yer bo
A KB Q23 A		MGEETV	SPLK O E	OKUBE ONO	PLACINGING
A SE SE659				QAQQAQ	PLUSTYZTIG
A SE SE725				• • • • • • • • • • •	• • • • • • • • • • • •
A SE SE753		MREEIA	SDDK O E	0 KG 0DD	Divor war
A SE SB853			drrk.yb	QKGQDP	PLVSLKSLFG
A SE SE889			• • • • • • • • • •	• • • • • • • • • • •	• • • • • • • • • •
A SE UGSE8		MGEEIA	CDDK V B	0	
A UG 92UG0		MREEIV	SPER.QE	QNNP	PSVSLKSLFG
A_UG_U455_		. MGEKMTSPA	VODI V	QNDQNP	PSVSLKSLFG
AC_IN_2130	FE	ETTDAI.	Auaya	DKEQT	PLVSLKSLFG
AC RW 92RW	ENFG	ETTPAL MGEEIASPL.	Qb	QKDRE	PLTSLKSLFG
AC_SE_SE94		MODELASEL.	ay	QKDRE	PLISLKSLFG
ACD_SE_SE8		FGEEITP			
ACG BE VI1		KEDAIDEC	S.QK.QE	QKDKELY	PLASLKSLFG
AD SE SE69		KEDAIDSS	PKQB	PROKGLYP	PLTSLKSLFG
AD SE SE71		FGEEIAP	.SQKQEQ	KDKELY	PLASLKSLFĢ
ADHK NO 97	••••••	TOPPIM			• • • • • • • • • • • • • • • • • • • •
ADK CD MAL	• • • • • • • • • • •	IGEEIT	SIQK.QE	OKDREPPP	PLVSLKSLFG
AG_BE_VI11	• • • • • • • • • • •	FGEEIK	PSQK.QE	QKDKEL.Y	PLASLKSLFG
AG NG 92NG	• • • • • • • • • • • • • • • • • • • •	MEEEIT	PSQK.QE	PRDTGLYP	PLTSLKSLFG
AGHU GA VI	• • • • • • • • • •	FGEEIAP	S.LK.QE	PREKESPP	L.TSLKSLFG
AGU CD Z32	• • • • • • • • • • • • • • • • • • • •	FGEEIA	PSPR.PE	PREKER.Y	PLTSLKSLFG
AJ BW BW21	• • • • • • • • •	TKEEITS	S.PK.QE	PRDKELYP	PLASLKSLFG
B AU VH AF	• • • • • • • • • •	FGEETA	PSPK.QE	GKDKEL.Y	PLTSLKSLFG
B_CN RL42	• • • • • • • • • • •	FGEETTTP	.SQKQE	PIDKELY	PLASLRSLFG
B_DE_D31 U	• • • • • • • • • •	FGEETTTP	.SQKQE	PIDKELY	PLASLKSLFG
B_DE_D31_U B_DE_HAN_U	• • • • • • • • • • •	FGEETATP	.FQKQE	PIDKELY	PLASLRSLFG
B_FR_HXB2_	• • • • • • • • • •	FGEATAP	.SQKQE	PIDKELY	PLASLKSLFG
B_GA_OYI	• • • • • • • • • • •	SGVETTTP		PIDKELY	PLTSLRSLFG
	• • • • • • • • • • • • • • • • • • • •	FGEETTTP		PIDKGLY	PLTSLRSLFG
B_GB_CAM1_	• • • • • • • • • •	FGEEKTTP	.SQKQE	PIDKELY	PLASLRSLFG
B_GB\GB8_A B_GB_MANC_	• • • • • • • • • • •	FGGETTTP		PINKEPY	PLASLRSLFG
	• • • • • • • • • •	FGEETTTP		PIDKELY	PLASLRPLFG
B_KR_WK_AF		FGEETTTP	.SQKQE	PIDKELY	PLASLRSLFG
B_NL_3202A B TW TWCYS	• • • • • • • • • • • •	FGEETTTP	.SQKQE	PRDKELY	PLASLRSLFG
B US BC LO	• • • • • • • • • • •	FGEQTTTP	.SQKQE	PIDKDLY	PLASLESLFG
	• • • • • • • • • • • • • • • • • • • •	FGEETTTP	.PQKQERE	DKEMY	PLASLRSLFG
B_US_DH123	• • • • • • • • •	FGEETATP	.SQKQE	PKELY	PLASLKSLFG
B_US_JRCSF	• • • • • • • • • •	FGEETATP		PIDKELY	PLTSLRSLFG
B_US_MNCG_	• • • • • • • • • • • • • • • • • • • •	FGEETTTP	.YQKQEKKQE	TIDKDLY	PLASLKSLFG
B_US_P896_	• • • • • • • • • • • • • • • • • • • •	FGEETTTP	.SQKQE	PIDKELY	PLASLRSLFG
B_US_RF_M1		FGEETTP	.SQKQE	KIDKELY	PLASLKSLFG
B_US_SF2_K B US WEAU1	• • • • • • • • • •	FGEEKTTP	.SQKQE	PIDKELY	PLTSLRSLFG
D NC MD32	• • • • • • • • • • • • • • • • • • • •	FREETTTP	.SQKQE	PIDKELY	PLTSLKSLFG
B_US_WR27_	• • • • • • • • • • • • • • • • • • • •	FGXETTTP	.SQKQE	PIDKELY	PLASLRSLFV
B_US_YU2_M	• • • • • • • • • • •	FGEETTTP	.SQKQE	PIDKELY	PLASLRSLFG
BF1_BR_93B	• • • • • • • • • •	FGEEVITP	.SQKQE	PIDK EMY	PLASI.RSI.FG
C_BR_92BR0	ESFR	FGEETTTPS.	RKQE	TIDKEL	PLTSLKSLFG
C_BW_96BW0	FE	ETTPVP	KQE	PKDRE	PLTSLKSLFG
C_BW_96BW1	• • • • • • • • • • • • • • • • • • • •	.EETTPAP	KOE	TKDRE	PLISLKSLFG
C_BW_96BW1	· · · · · FE · · ·		KQE	PKDREP	PLASLKSLFG
C_BW_96BW1	FE	ETTPAP	KQE	PKDRE	PLISLKSLEG
C_ET_ETH22	PIAPPPESER	FEEATPSPK.	QE	LKDRE	ALTSLKSLEG
C_IN_93IN1	FE	ETTPAP	KQE	PKDRE	PLTSLKSLFG
C_IN_93IN9	FE	ETPPAP	KQE	PKDRE	PLTSLRSLFG
C_IN_93IN9	· · · · · FE · · ·	ETTPAL	KQE	PKDRE	PLTSLKSLEG
C_IN_94IN1	· · · · · · FE · · ·	ETPPAP	KQE	PKERE	PLTSLRSLEG
C_IN_95IN2	· · · · · · FE · · ·	ETTPAP	KOE	PKDRE	PLTSLPSLEC
CRF01_AE_C	• • • • • • • • • • • • • • • • • • • •	MGEEIT	SFPK.QE	QKDKEHPS	PLVSLKSLFG

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CRF01_AE_C
           ..... MGEEIT.... SFPK.Q...E QKDKK..QPP PLVSLKSLFG
CRF01_AE_C
           ..... MGEEIT.... SFSR.Q...E QKDRE..HPP PLVSLKSLFG
CRF01 AE T
           ..... MGEETT.... .SLLKQ...E QKDKE..HHP PLVSLKSLFG
CRF01 AE T
           ..... MGEEIT.... SLPK.Q...E QKDKD..PPP .LVSLKSLFG
CRF01 AE T
           ..... MGEE..... QKDKE..HPP PSVSLKSLFG
           ..... MGEETT.... SSLK.Q...E QKDKE..PPP PLISLKSLFG
CRF01 AE T
           ..... MGEEITGEEI TSLPKQ...E QKDKE..HPP PLVSLKSLFG
CRF01 AE T
CRF01 AE T
           ..... MGEEIT.... SFLK.Q...E QKDKE..HPP PSVSLKSLFG
           ..... MGEEIT.... SPPK.Q...E ARDQG..LYP PLASLKSLFG
CRF02_AG_F
CRF02_AG_F
           ..... MGEEIT.... SPPK.Q...E PRDQG..LYP PLASLKSLFG
           ..... TREEITSS.. ..PQQE.... PRDKG..LYP PLTSLKSLFG
CRF02_AG_G
           ..... MGEEIP.... PSPQ.Q...E PRDKG..LYP PLTSLKSLFG
CRF02_AG_N
           ..... IGEEIT.... SSQK.Q...E PGDKG..LYP PLASLKSLFG
CRF02 AG S
CRF02 AG S
           ..... MGEEIT.... SSPK.Q...E PGDKG..LYP PLTSLKSLFG
CRF03 AB R
           ..... MGEEIT.... PSLK.Q...E QKDRE..QHP PSISLKSLFG
CRF03 AB R
           ..... MGEEIT.... PSLK.Q...E QKDRG..QHP PSISLKSLFG
           ..... RKEETTS... S.LK.Q...E PRDKE..LYP .LTSLKSLFG
CRF04_cpx
CRF04_cpx_
           ..... MKEETTS... S.PK.Q...E PRDKE..LYP .LTSLKSLFG
CRF04_cpx_
           ..... MKEETTS... S.PK.Q...E QRDKE..LYP .ITSLKSLFG
CRF05_DF_B
           ..... FGEEIAS... .SPKQE...Q KDEG...LYP PLASLKSLFG
           ...... FGEEITP... .SPKQE...Q KDEG...KYP PLASLKSLFG
CRF05_DF_B
           ..... FGEEIAP... S.PK.Q...E SKEKEEKGLY PLASLKSLFG
CRF06_cpx_
           ...... FGEETAP... S.PE.Q...K PKEKE...LY PLTSLRSLFG
CRF06_cpx_
CRF06_cpx_
           ..... FGEETAP... S.LK.Q...E PKEKEKE.LY PLASLKSLFG
CRF06_cpx_
           ..... FGEEIAP... S.PK.Q...E PKEKE...LY PLASLKSLFG
           ..... FGEEIAP... .SPK.Q...E PKEKEK.ELY PLTSLKSLFG
CRF11_cpx_
           ..... FGEETTP... .SPK.Q...E PKEK...ELY PITSLKSLFG
CRF11 cpx
           ..... FGEEITP... .SQKQEQK.. DKDK...ELY PLASLKSLFG
D CD 84ZR0
          ...... FGEEITP... .SQKQE...Q KDK....ELY PLTSLKSLFG
...... FGEEITP... .SQKQE...Q KDK....ELY PLASLKSLFG
D_CD ELI K
D_CD_NDK M
           ..... LGEEITP... . PQKQE...Q KDK....ELY PLTSLKSLFG
D_UG_94UG1
           .....FR... .EEITPSP.....KQE.... QKDGEL..YP PLASLKSLFG
F1_BE_VI85
F1_BR_93BR
           .....FG... .EETTPSP.. ...KQE.... QKDEGL..YP PLASLKSLFG
P1 FI FIN9
           .....IR... .EEVTPSP.. ...RQE.... QKEEGQ..YP PLASLKSLFG
F1_FR_MP41
           .....FK... .EEITPSP.....KQE.... QKDEGQGLYP PLASLKSLFG
F2_CM_MP25
           .....FG... .EEIAPSP.....KQE.... QKDKEQ..VP PLISLKSLFG
           .....FG... .EEINPSP.. ...RQE.... TKDKGQ..EP PLTSLKSLFG
F2KU_BE_VI
          ..... FGEEIAP... S.PK.Q...E QKEKE..LYP L.SSLKSLFG
G BE DRCBL
          ..... FGEEIAP... S.PK.Q...E PKEKE..LYP L.TSLKSLFG
G NG 92NG0
          ..... FGEEIAP... S.PK.Q...E MKEKE..LYP ...SLKSLFG
G SE SE616
H_BE_VI991
          .....FG... .EEITPSP.. ...RQE.... LKEQE....P PLTSLRSLFG
H_BE_VI997
           .....FG... EEMTSSP.....KQE.... LKDKE....P PFASLKSLFG
H_CF_90CF0
           .....FG... .EEMTPSP.. ...KQEQ... LKDKE....P PLASLRSLFG
           .....FG... ..EEIPSP.. ...KQE.... PKDKE...LY PLTSLRSLFG
J SE SE702
J SE SE788
           .....LG... ..EEIPSP.. ...KQE.... PKDKE...LY PLTSLKSLFG
K CD EQTB1
           .....FG... .EKITPSL.. ... RQE.... MKDQEQ..GP PLTSLKSLFG
          .....FG....EEITPSP.....RQE.... TKDKEQ..SP PLTSLKSLFG
K_CM MP535
N CM YBF30
          .....FQ... . EEKSTQ.. GKEMQE...N QERTENSLYP PLTSLRSLFG
O CM ANT70
          .....LY PFASLKSLFG
          .....LY PFASLKSLFG
O CM MVP51
          O_SN_99SE
           O SN 99SE
U_CD___83C
          .....FG... .EETTPSP.. ...KQE.... PRDKESL.YP PLTSLKSLFG
          551
00BW0762 1
          SDPLSO
00BW0768 2
          SDPLSO
00BW0874_2
          NDPLSQ
00BW1471 2
          SDPLSO
00BW1616_2
          SDPLSQ
```

```
00BW1686_8 SDPLSQ
00BW1759_3
            SDPLSQ
00BW1773_2
            SDPLSQ
00BW1783 5
            SDPLSQ
00BW1795 6
            SDPLSQ
00BW1811_3
            SDPLSQ
00BW1859 5 SDPLSQ
00BW1880_2 NDPLSQ
00BW1921_1 SDPLSQ
00BW2036_1 SDPLSQ
00BW2063_6 NDPLSQ
00BW2087_2
            SDPLSQ
00BW2127_2
            SDPLSQ
00BW2128_3
            SDPWSQ
00BW2276_7
            SDPLSQ
00BW3819 3
            SDPLSQ
00BW3842 8
            SDPLSQ
00BW3871_3
            SDPLSQ
00BW3876_9
            SDPLSQ
8_88£W800
           SDPLSQ
00BW3891_6
           SDPLSQ
00BW3970_2
            SDPLSO
00BW5031 1
            SDPLSO
 96BW01B21
            SDPLSQ
  96BW0407
            NDPLSQ
  96BW0502
           SGPLSQ
 96BW06 J4
           SDPLSQ
 96BW11 06 SDPLSO
  96BW1210 NDPLSQ
 96BW15B03
           SDPLSQ
 96BW16_26
           NDPLSQ
 96BW17A09
            SDPLSO
 96BWM01_5
            SDPLSQ
 96BWMO3_2
            SDPLSO
98BWMC12_2
            NDPLSQ
98BWMC13_4
            SDPLSQ
98BWMC14_a
            NDPLSQ
98BWMO14_1
            SDPLSQ
98BWM018 d
            SDPLSQ
98BWMO36_a
            SDPLSQ
98BWM037_d
            SDPLSQ
99BW3932_1
            SDPLSQ
99BW4642_4
            SDPLSQ
99BW4745 8
            SDPLSQ
99BW4754_7
            NDPLSQ
99BWMC16_8 GDPLSQ
A2_CD_97CD NDLLSQ
A2_CY_94CY NDPLLQ
A2D 97KR NDPLLO
A2G_CD_97C
           . . . . . .
A_BY_97BL0 NDPLSQ
A_KE_Q23_A NDLLSQ
A_SE_SE659
           . . . . . .
A_SE_SE725
            . . . . . .
A_SE_SE753
           NDLLSO
A SE SE853
A_SE_SE889
A SE UGSE8
           NDLLSQ
A UG 92UG0
           NDLLSQ
A_UG_U455
           NDPLSQ
```

```
AC_IN_2130
             SDPLSQ
 AC_RW_92RW
             NDPLSQ
 AC SE SE94
              . . . . .
 ACD_SE_SE8
             NDP...
 ACG_BE_VI1
             NDP...
 AD SE SE69
             NDP...
 AD SE SE71
             . . . . . .
 ADHK_NO_97
             NDPLSO
 ADK_CD_MAL
             NDQLSQ
 AG_BE_VI11
             NDP...
 AG_NG_92NG
             NDP...
 AGHU_GA_VI
             SDP...
 AGU_CD_Z32
             SDP...
 AJ_BW_BW21
             SDP...
 B_AU_VH_AF
             NDPSSQ
B_CN_RL42_
             NDPSSQ
B DE D31 U
             NDPSSQ
B DE HAN U
             SDPSSO
B_FR_HXB2_
             NDPSSQ
B_GA_OYI_
             NDPSSQ
B_GB_CAM1_
             NDPSSQ
B_GB_GB8_A
             NDPSSQ
B_GB_MANC_
B_KR_WK_AF
             NDPSSO
             NDPSSQ
B_NL_3202A
             NDPSSQ
B_TW_TWCYS
             NDPSSQ
B US BC LO
             NDPSSQ
B US DH123
             NDP...
B_US JRCSF
             NDPSSO
B_US_MNCG_
             NDPLSQ
B_US_P896_
             NDPSSQ
B_US_RF_M1
            NDPSSQ
B_US_SF2_K
             NDPSSQ
B US WEAU1
             NDPSSO
B_US_WR27_
             NDPSSQ
B_US_YU2_M
            SDPSSQ
BF1_BR_93B
            NDPSSQ
C BR 92BR0
            SDPLST
C_BW 96BW0
             SDPLSO
C_BW_96BW1
             SDPLSO
C_BW_96BW1
            NDPLSO
C_BW_96BW1
            SDPLSQ
C_ET_ETH22
            NDHLLQ
C_IN_93IN1
            SDLLSQ
C_IN_93IN9
            SDPLSQ
C_IN_93IN9
            SDPLSQ
C_IN_94IN1
            SDPLSQ
C_IN_95IN2
            SDPLSQ
CRF01_AE_C
            NDPLSQ
CRF01_AE_C
            NDPLSQ
CRF01_AE_C
            NDPLSQ
CRF01_AE_T
            NDPSSO
CRF01_AE_T
            NDPLSQ
CRF01_AE_T
            NDPLSQ
CRF01_AE_T
CRF01_AE_T
            NDPLSQ
            NDPLSQ
CRF01_AE T
            NDPLSQ
CRF02_AG_F
            NDP...
CRF02_AC_F
            NDP...
CRF02_AG_G
            NDP...
```

SOWSEDS TIESON

```
CRF02_AG_N NDP...
 CRF02_AG_S
              NDP...
CRF02_AG_S NDPYSQ
CRF03_AB_R DDPLSQ
CRF03_AB_R NDPLSQ
CRF04_cpx_
             SDPLSQ
CRF04_cpx_ NHPLSQ
CRF04_cpx_
             SDPLSR
CRF05_DF_B NDPLSQ
CRF05_DF_B NDPLSQ
CRF06 cpx
CRF06 cpx
CRF06 cpx
CRF06 cpx
             SDP...
             NDP...
             NDP...
             SDP...
CRF11_cpx_
             SDP...
CRF11_cpx_
             SDPLSQ
D_CD_84ZR0
             NDPLSQ
D_CD_ELI_K
             NDPLSQ
D_CD_NDK_M
             NDPSSQ
D_UG_94UG1
             NDPLSQ
F1_BE_VI85
F1_BR_93BR
             NDP...
             NDP...
F1_FI_FIN9
F1_FR_MP41
             NDP...
             SDP...
F2_CM_MP25
             SDQ...
F2KU_BE_VI
            SDPLLQ
G BE DRCBL NDQ...
G_NG_92NG0 SDP...
G SE SE616 SDP...
H_BE_VI991 NDQ...
H_BE_VI997
             NDPLSQ
H_CF_90CF0
             SDPLLQ
J_SE_SE702
             SDPLSO
J_SE_SE788
             SDPLSO
K_CD_EQTB1
             SDPLSQ
K_CM_MP535 NDPLSQ
N_CM_YBF30 NDPSSQ
O_CM ANT70
             TDQ...
O CM MVP51
             TDQ...
O_SN_99SE_
             TDQ...
O_SN_99SE_
             TDQ...
U_CD__83C SDPSLQ
```

Table 12. HIV Env Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

Name:	00BW0762_1	Len:	962	Check:	4645	Weight:	1.00
Name:	· -	Len:	962	Check:	9565	Weight:	
Name:	00BW0874_2	Len:	962	Check:	7745		
Name:	_	Len:	962	Check:	9593		
Name:	00BW1616_2	Len:	962	Check:	792	Weight:	1.00
Name:	00BW1686_8	Len:	962	Check:	3744	Weight:	1.00
Name:		Len:	962	Check:	9808	Weight:	1.00
Name:	00BW1773_2	Len:	962	Check:	3500	Weight:	
Name:	00BW1783_5	Len:	962	Check:	9684	Weight:	
Name:	00BW1795_6	Len:	962	Check:	8410		
Name:	00BW1811_3	Len:	962	Check:	2068		
Name:	00BW1859_5	Len:	962	Check:	5692	Weight:	1.00
Name:	00BW1880_2	Len:	962	Check:	1901	Weight:	1.00
Name:	00BW1921_1	Len:	962	Check:	5923	Weight:	1.00
Name:	00BW2036_1	Len:	962	Check:	7035	Weight:	1.00
Name:	.00BW2063_6	Len:	962	Check:	4853		1.00
Name:	00BW2087_2	Len:	962	Check:	2085		1.00
Name:	00BW2127_2	Len:	962	Check:	4015	_	1.00
Name:	00BW2128_3	Len:	962	Check:	5884	_	1.00
Name:	00BW2276_7	Len:	962	Check:	8913	Weight:	1.00
Name:	00BW3819_3	Len:	962	Check:	9390	Weight:	1.00
Name:	00BW3842_8	Len:	962	Check:	8867		1.00
Name:	00BW3871_3	Len:	962	Check:	7069	_	1.00
Name:	00BW3876_9	Len:	962	Check:	4761		1.00
Name:	00BW3886_8	Len:	962	Check:	7681	Weight:	1.00
Name:	00BW3891_6	Len:	962	Check:	379	Weight:	1.00
Name:	00BW3970_2	Len:	962	Check:	8001		1.00
Name:	00BW5031_1	Len:	962	Check:	4902		1.00
Name:	96BW01B21	Len:	962	Check:	5774	Weight:	1.00
Name:	96BW0407	Len:	962	Check:	4260	Weight:	1.00
Name:	96BW0502	Len:	962	Check:	4658	Weight:	1.00
Name:	96BW06_J4	Len:	962	Check:	9749		1.00
Name:	96BW11_06	Len:	962	Check:	4328		1.00
Name:	96BW1210	Len:	962	Check:	3855	Weight:	1.00
Name:	96BW15B03	Len:	962	Check:	9133	Weight:	1.00
Name:	96BW16_26	Len:	962	Check:	5 W		1.00
Name:	96BW17A09	Len:	962	Check:	6458	-	1.00
Name:	96BWMO1_5	Len:	962	Check:	9487		1.00
Name:	96BWMO3_2	Len:	962	Check:	8766		1.00
Name:	98BWMC12_2	Len:	962	Check:	2722	Weight:	1.00
Name:	98BWMC13_4	Len:	962	Check:	2526		1.00
Name:	98BWMC14_a	Len:	962	Check:	7761	Weight:	1.00
Name:	98BWM014_1	Len:	962	Check:		Weight:	1.00
Name:	98BWM018_d	Len:	962	Check:	279	Weight:	1.00
Name:	98BWMO36_a	Len:	962	Check:		Weight:	1.00
Name:	98BWM037_d	Len:	962	Check:		Weight:	1.00
Name:	_	Len:	962		3527		1.00
Name:	·	Len :.	962	Check:			1.00
Name:	99BW4745_8	Len:	962	Check:	8117		1.00
Name:		Len:	962	Check:	5709	Weight:	1.00
Name:		Len:	962	Check:		Weight:	1.00
Name:	— . — . —	. Len:	962	Check:	2892	Weight:	1.00
	A2_CY_94CY	Len:	962	Check:	8628	Weight:	1.00
Name:		Len:	962	Check:		Weight:	1.00
Name:	A2G_CD_97C	Len:	962	Check:		Weight:	1.00
Mante:	A_BY_97BL0	Len:	962	Check:	4291	Weight:	1.00

```
Name: A_KE Q23 A
                         Len:
                                 962
                                      Check: 1190
                                                    Weight:
                                                               1.00
Name: A_SE_SE659
                         Len:
                                 962
                                      Check: 6674
                                                    Weight:
                                                               1.00
Name: A_SE_SE725
                         Len:
                                 962
                                      Check: 4925
                                                    Weight:
                                                               1.00
Name: A SE SE753
                         Len:
                                 962
                                      Check: 2482
                                                    Weight:
                                                               1.00
Name: A SE SE853
                                      Check: 1860
                         Len:
                                 962
                                                    Weight:
                                                               1.00
Name: A SE SE889
                         Len:
                                 962
                                      Check: 2102
                                                    Weight:
                                                               1.00
Name: A SE UGSE8
                         Len:
                                 962
                                      Check: 5063
                                                    Weight:
                                                               1.00
Name: A UG 92UG0
                         Len:
                                 962
                                      Check: 6685
                                                    Weight:
                                                               1.00
Name: A_UG U455
                         Len:
                                 962
                                      Check: 8657
                                                    Weight:
                                                               1.00
Name: AC_IN_2130
                         Len:
                                 962
                                      Check: 7784
                                                    Weight:
                                                               1.00
Name: AC_RW_92RW
                         Len:
                                 962
                                      Check: 4676
                                                    Weight:
                                                               1.00
Name: AC_SE_SE94
                         Len:
                                 962
                                      Check: 2949
                                                    Weight:
                                                               1.00
Name: ACD_SE SE8
                         Len:
                                 962
                                      Check: 1464
                                                    Weight:
                                                               1.00
Name: ACG BE VI1
                         Len:
                                 962
                                      Check: 2980
                                                    Weight:
                                                               1.00
Name: AD SE SE69
                         Len:
                                 962
                                      Check: 8959
                                                    Weight:
                                                               1.00
Name: AD_SE SE71
                         Len:
                                 962
                                      Check: 7056
                                                    Weight:
                                                               1.00
Name: ADHK NO 97
                                      Check: 487
                         Len:
                                 962
                                                   Weight:
                                                              1.00
Name: ADK CD MAL
                         Len:
                                      Check: 2555
                                 962
                                                    Weight:
                                                               1.00
Name: AG BE VI11
                         Len:
                                 962
                                      Check: 6342
                                                    Weight:
                                                               1.00
Name: AG NG 92NG
                         Len:
                                 962
                                      Check: 1272
                                                    Weight:
                                                               1.00
Name: AGHU GA VI
                         Len:
                                 962
                                      Check: 1974
                                                    Weight:
                                                               1.00
Name: AGU CD Z32
                         Len:
                                 962
                                      Check: 4356
                                                    Weight:
                                                               1.00
Name: AJ BW BW21
                         Len:
                                 962
                                      Check: 9995
                                                    Weight:
                                                               1.00
Name: B AU VH AF
                         Len:
                                 962
                                      Check: 5833
                                                    Weight:
                                                               1.00
Name: B_CN_RL42
                                      Check: 4092
                         Len:
                                 962
                                                    Weight:
                                                               1.00
Name: B_DE_D31 U
                         Len:
                                 962
                                      Check: 5486
                                                    Weight:
                                                               1.00
Name: B DE HAN U
                                      Check: 3480
                         Len:
                                 962
                                                    Weight:
                                                               1.00
Name: B FR HXB2
                         Len:
                                962
                                      Check: 6939
                                                    Weight:
                                                               1.00
Name: B GA OYI
                                      Check: 9780
                         Len:
                                962
                                                    Weight:
                                                               1.00
Name: B_GB_CAM1_
                         Len:
                                      Check: 9716
                                962
                                                    Weight:
                                                               1.00
Name: B_GB GB8 C
                                      Check: 4180
                         Len:
                                 962
                                                    Weight:
                                                               1.00
Name: B_GB_MANC
                         Len:
                                 962
                                      Check: 9762
                                                    Weight:
                                                               1.00
Name: B_KR_WK_AF
                         Len:
                                962
                                      Check: 6641
                                                    Weight:
                                                               1.00
Name: B_NL_3202A
                         Len:
                                962
                                      Check: 7168
                                                    Weight:
                                                               1.00
Name: B TW TWCYS
                         Len:
                                      Check: 3591
                                962
                                                    Weight:
                                                               1.00
Name: B_US_BC_LO
                                      Check: 7266 Weight:
                         Len:
                                962
                                                               1.00
Name: B_US_DH123
                         Len:
                                962
                                      Check: 6905
                                                    Weight:
                                                               1.00
Name: B US JRCSF
                                      Check: 9381 Weight:
                         Len:
                                962
                                                               1.00
Name: B US MNCG
                         Len:
                                962
                                      Check: 9951
                                                    Weight:
                                                               1.00
Name: B US P896
                         Len:
                                      Check: 5855
                                962
                                                    Weight:
                                                               1.00
Name: B US RF Ml
                                      Check: 6075
                         Len:
                                962
                                                    Weight:
                                                               1.00
Name: B_US_SF2_K
                         Len:
                                962
                                      Check: 1434
                                                    Weight:
                                                               1.00
Name: B_US_WEAU1
                         Len:
                                962
                                      Check: 5451
                                                    Weight:
                                                               1.00
Name: B_US_WR27_
                         Len:
                                962
                                      Check: 4262
                                                    Weight:
                                                               1.00
Name: B US YU2 M
                         Len:
                                962
                                      Check: 5841
                                                    Weight:
                                                               1.00
Name: BF1 BR 93B
                                      Check: 5506
                         Len:
                                962
                                                    Weight:
                                                               1.00
Name: C_BR_92BR0
                         Len:
                                962
                                      Check: 8769
                                                    Weight:
                                                               1.00
Name: C_BW_96BW0
                         Len:
                                962
                                      Check: 6197
                                                    Weight:
                                                               1.00
Name: C BW 96BW1
                         Len:
                                962
                                      Check: 8144
                                                    Weight:
                                                               1.00
Name: C BW 96BW1
                         Len:
                                962
                                      Check: 1160
                                                    Weight:
                                                               1.00
Name: C_BW 96BW1
                         Len:
                                962
                                      Check: 2736
                                                    Weight:
                                                               1.00
Name: C_ET_ETH22
                                      Check: 8219
                         Len:
                                962
                                                    Weight:
                                                               1.00
Name: C_IN_93IN1
                         Len:
                                962
                                      Check: 4068
                                                    Weight:
                                                               1.00
Name: C_IN_93IN9
                         Len:
                                962
                                      Check: 3674
                                                    Weight:
                                                               1.00
Name: C_IN_93IN9
                         Len:
                                962
                                      Check: 1581
                                                    Weight:
                                                               1.00
Name: C_IN_94IN1
Name: C_IN_95IN2
                         Len:
                                962
                                      Check: 9352
                                                    Weight:
                                                               1.00
                         Len:
                                      Check: 6988
                                962
                                                    Weight:
                                                               1.00
Name: CRF01_AE_C
                         Len:
                                962
                                      Check: 8684
                                                    Weight:
                                                               1.00
Name: CRF01 AE C
                         Len:
                                962
                                      Check: 3342
                                                    Weight:
                                                               1.00
Name: CRF01 AE C
                        Len:
                                962
                                      Check: 5017
                                                    Weight:
                                                               1.00
```

```
Name: CRF01_AE_T
                        Len:
                               962
                                    Check: 9124 Weight:
                                                            1.00
 Name: CRF01_AE_T
                        Len:
                               962
                                    Check: 2718
                                                 Weight:
                                                            1.00
 Name: CRF01 AE T
                        Len:
                               962
                                    Check: 2104
                                                 Weight:
                                                            1.00
 Name: CRF01 AE T
                        Len:
                               962
                                    Check: 8495
                                                 Weight:
                                                            1.00
 Name: CRF01 AE T
                                    Check: 4076
                        Len:
                               962
                                                Weight:
                                                            1.00
                        Len:
 Name: CRF01 AE T
                               962
                                    Check: 948 Weight:
                                                           1.00
 Name: CRF02 AG F
                        Len:
                               962
                                    Check: 9298
                                                 Weight:
                                                           1.00
 Name: CRF02 AG F
                        Len:
                               962
                                    Check: 9278
                                                 Weight:
                                                            1.00
 Name: CRF02_AG_G
                        Len:
                               962
                                    Check: 4373
                                                 Weight:
                                                           1.00
 Name: CRF02 AG N
                        Len:
                               962
                                    Check: 8955 Weight:
                                                            1.00
 Name: CRF02_AG_S
                                    Check: 252 Weight:
                        Len:
                               962
                                                           1.00
 Name: CRF02_AG_S
                        Len:
                                    Check: 5147 Weight:
                               962
                                                           1.00
 Name: CRF03_AB_R
                        Len:
                               962
                                    Check: 2239 Weight:
                                                           1.00
 Name: CRF03 AB R
                        Len:
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51
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A BY 97BLO
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AC RW 92RW
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AC SE SE94
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CRF01 AE T
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98BWMC13 4
98BWMC14_a MWRNDMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLDCTNV T.....
98BWM014_1
           MWENDMVDQM HQDIISLWDE SLKPCVKLTP LCVTLNCRNA NLN.....
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLTCTNA TKNVTN....
98BWM018_d
           MWKNDMVDQM HEDVISIWDQ SLKPCVKLTP LCVTLNCSNV N......
98BWM036 a
           MRDNDMVDQM HEDIINLWDQ SLKPCVRLTP LCVTLNCKDA SVN.....
98BWM037 d
99BW3932_1
           MWKNDMVDQM HEDMIRLWDQ SLKPCVKLTP LCVTLKCREV N......
99BW4642 4
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLKCTNV N......
99BW4745 8
           MWKNDMVDQM HEDVISLWDQ SLKPCVKLTP LCVTLICSNN I......
99BW4754 7
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLNCNKV TV......
99BWMC16 8
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLNCVNV TKNVTK....
           MWKNNMVEQM HADIISLWDQ SLKPCVKLTP LCVTLNCSNA NTTNT.....
A2 CD 97CD
A2_CY_94CY
          MWKNNMVEQM QEDIISLWDQ SLKPCVKLTP LCVILNCSNA NTSTH.....
A2D___97KR
          MWKNGMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCSRV KNTIS.....
A2G CD 97C
          MWKNDMVEQM HVDIISLWDQ SLKPCVKLTP FCVTLNCTNA TFPNA....
A_BY_97BL0
           MXKNNXVEQM QTDIISL, DQ SLKPCVKLTP LCVTLNCAEP NSTRS.....
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLHCTNV TSV.....
A KE Q23 A
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCTNV ......
A SE SE659
A_SE_SE725 MWKNSMVEQM HTDIISLWDE SLKPCVKLTP LCVTLNCTNA ......
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MWKNYMVEQM HTDIISLWDQ SLEPCVKLTP LCVTLECHYN ITV.....
A SE SE753
           MWKNSMVEQM HTDIISLWDQ SLIPCVKLTP LCVTLECNDY NYN.....
A SE SE853
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCSSV TN......
A_SE_SE889
           MWKNNMVEQM HTDIISLWDQ SLKPCVQLTP LCVTLNCSNN VTA.....
A_SE_UGSE8
           MWKNNMVEQM HTDIISLWDQ SLKPCVQLTP LCVTLDCSYN ITN.....
A_UG_92UG0
           MWKNNMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLDCHNI TIN.....
A UG U455
           MWKNSMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCSNV NG.....
AC IN 2130
AC RW 92RW
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLECNNI TNVNN....
AC SE SE94
           IWKNYMVEQM HQDIISLWDQ SLKPCVKLTP LCVTLNCRDA TV......
ACD_SE_SE8 MWKNNMVEQM HTDIISLWDQ SLQPCVKLTP LCVTLNCTNV TIT.....
ACG BE VII MWKNDMVDQM HQDIISLWDE SLKPCVKLTP LCVTLNCSNV TAIN.....
AD SE SE69 MWKNNMVEQM HTDIISLWDQ SLKPCVQLTP LCVTLNCNNV TNKIN....
AD_SE_SE71 MWKNNMVKQM HTDIISLWDQ SLQPCVKLTP LCVTLHCNDT ..N.....
           MWENNMVDQM HTDIISLWDQ SLKPCVKLTP LCVTLNCTDP AN.....
ADHK NO 97
ADK_CD_MAL MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTNV NGTAVNG.TN
AG BE VI11
           MWKNNMVDQM HEDIISLWDE SLKPCVKLTP LCVTLTCTNV NCTNN....
           MWKNNMVEQM HEDIISLWDE SLKPCVKLTP LCVTLNCTNV NCNSN...VT
AG NG 92NG
AGHŲ GA VI
           MWKNNMVEQM HTDIISLWDQ SLKPCVQITP LCVTLECSKI N.....
AGU CD Z32
           MWKNNMVEQM HEDVISLWDQ SLKPCVKLTP LCVTLSCSDI R......
AJ BW BW21
           IWKNDMVEQM QEDIISVWDE SLKPCVKLTP LCVTLNCTNA TVSNT.....
           MWKNNMVEQM HEDIISLWDQ SLKPCVQLTP LCVTLNCTDE LT.....
B AU VH AF
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTNL K.....
B_CN_RL42
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDL K.....
B DE D31 U
B_DE_HAN_U MWKNDMVEQM QEDIISLWDQ SLKPCVKLTP LCVTLKCTDY N.......
B_FR_HXB2_
           MWKNDMVEQM HEDIISLWDQ SLKPCVKLTP LCVSLKCTDL K.....
           MWKNNMVEQM QEDIISLWDQ SLKPCVKLTP LCVTLDCTDV NTTSSS....
B_GA OYI
B_GB_CAM1_
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLICTNV NN.....
B_GB_GB8_C MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDL R.....
           MWKNNMVEQM QEDVISLWDQ SLKPCVKLTP LCVTLDCTDY VG.....
B GB MANC
B_KR_WK_AF MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLKCTDL NDTNTN....
B_NL_3202A MWKNNMVEQM HEDIINLWDQ SLKPCVKLTP LCVTLNCTDF G.......
B_TW_TWCYS MWKNNMADQM QEDIISLWDE SLKPCVELTP LCVTLKCNDT .....
           MWKNNMVEQM QEDIISLWDQ SLKPCVKLTP LCVTLNCTDE LKNA.....
B_US_BC_L0
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLHCTDL K.....
B_US_DH123
B_US_JRCSF MWKNNMVEQM QEDVINLWDQ SLKPCVKLTP LCVTLNCKDV .....
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDL R......
B_US_MNCG_
           MWKNNMVDQM HEDIISLWDE SLKPCVKLTP LCVTLNCTNL .....
B_US_P896
B_US_RF_M1
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDA NLN.....
B_US_SF2_K
           MWKNNMVEQM QEDIISLWDQ SLKPCVKLTP LCVTLNCTDL G.....
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTNV NVTN.....
B US WEAU1
B US WR27
           MWKNNMXEQM HEDIIXLWDQ SLKPCVKLTP LCVTLNCTDV .....
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDL .....
B US YU2 M
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLRCSNA TT.....
BF1_BR 93B
           MWENDMVEQM HQDIISLWDQ SLKPCVKLTP LCVTLHCSNR T.....
C_BR_92BR0
C_BW_96BW0
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTEV NGTSDSS...
           MWENDMVNQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTNV TV......
C BW 96BW1
C_BW_96BW1
C_BW_96BW1
           MWKNDMVDQM HEDIISLWDE SLKPCVKLTP LCVTLNCSNN VTR.....
           MWKNDMVDQM HEDIISLWDQ SLKPCVKLTP LCVTLKCTNY ST.....
C_ET_ETH22
           MWKNDMVEQM HQDIISLWDQ GLKPCVKLTP LCVTLNCNAI KNNTKVT...
C IN 93IN1
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C IN 931N9
           MWKNDMVNQM HEDVISLWDQ SLKPCVKLTP LCVTLECKNV K.....
           MWKNDMVNQM HEDVISLWDQ SLKPCVKLTP LCVTLECSEY NGTSKAN...
C IN 931N9
           MWKSDMVNQM HEDVISLWDQ SLKPCVKLTP LCVTLECGNV T.....
C IN 94IN1
           MWKNDMVNQM HEDVISLWDQ SLKPCVKLTP LCVTLECRNV NST.....
C IN 951N2
CRF01 AE C
           MWKNNMVEQM QEDVISLWDQ SLKPCVKLTP LCVTLHCTKA KLNDTYN...
CRF01_AE_C
           MWKNNMVEQM QEDVISLWDQ SLQPCVKLTP LCVTLHCTKA SFTNATS...
CRF01_AE_C
           MWKNNMVEQM QEDVISL.DQ SLKPCVKLTP LCVTLDCTKA DFYTTKF...
CRF01_AE_T
           MWKNNMVEQM QEDVISLWDQ SLQPCVKLTP LCVTLHCTTA KLTNVTN...
CRF01_AE_T
           MWKNNMVEQM QEDVISLWDQ SLKPCVKLTP LCVTLNCTNA NLTNVNN...
           MWKNNMVEQM QEDVISLWDQ SLKPCVKLTP LCVTLNCTNA NWTNANV...
CRF01_AE T
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MWKNNMVBQM QEDVISLWDQ SLKPCVKLTP LCVTLNCTTA NFTNFNL...
 CRF01 AE T
            MWKNNMVEQM QEDVISLWDQ SLKPCVKLTP LCVTLNCTNA NLTNGSS...
 CRF01 AE T
            MWKNKMABQM QEDVISLWDQ SLKPCVKLTP LCVTLNCTNV NATNVSN...
 CRF01 AE T
            MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLDCHNV NSS.....
 CRF02 AG F
            MWKNNMVEQM HEDIISLWDQ SLKPCVELTP LCVTLDCYNV SS......
 CRF02 AG F
 CRF02 AG G MWKNNMVEQM HVDIISLWDQ SLKPCVKLTP LCVTLDCQNF KN.....
 CRF02 AG N MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLDCHNF NN......
 CRF02_AG_S
            MWKNSMVEQM HEDIISLWDQ SLKPCVQLTP LCVTLHCQDN LT.....
 CRF02_AG_S
            MWKNNMVEQM HVDIISLWDQ SLKPCVKLTP LCVTLECHNY NYT.....
            MGKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDL KK.....
 CRF03 AB R
            MGKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTEV KT.....
 CRF03 AB R
            MWKNDMVEQM HEDIISLWNE GLKPCAKLTS LCVTFTCINA T.....
 CRF04_cpx_
            MWENSTVEQM HEDIISLWDE GLKPCVKLTP LCVALNCSNA TIIINS....
 CRF04_cpx_
 CRF04_cpx_
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 CRF05 DF B
           MWKNDMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCTDF KA.....
            MWKNNMVEQM HADIISLWDQ SLKSCVKLTP LCVTLNCTDA TS.....
 CRF05 DF B
            MWKNNMVDQM HEDIISLWDE SLKPCVKLTP LCVTLTCTNA TLGNKTLGNN
 CRF06_cpx_
            MWENHMVEQM HEDIISLWDE SLKPCVKLTP LCVTLICTNI NITSTNS...
 CRF06_cpx
CRF06_cpx_
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CRF06_cpx_
            MWKNNMVEQM HEDIISLWEE SLKPCVKLTP LCVTLNCTNV NAT.....K
            MWKNNMVEQM HEDIISLWDE SLKPCVKLTP LCVTLNCAEV TS.....
CRF11_cpx_
            MWKNNMVEQM HEDVISLWDE SLKPCVKLTP LCVALNCTDA R.....
CRF11_cpx_
D_CD_84ZR0
            MWKNNMVDQM HEDIIŞLWDQ SLKPCVKLTP RCVTLNCTDA SRN.....S
            MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCSDE LRNNG....T
D CD BLI K
D CD NDK M
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTDE LRN.....S
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLNCTNW VTD.....
D UG 94UG1
           MWKNNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCTNA TN......
F1 BE VI85
F1_BR_93BR MWENNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLDCRNI AT......
F1_FI_FIN9
           MWENDMVEQM HKDIISLWDQ SLKPCVKLTP LCVTLNCTNA TT......
           MWKNNMVEQM HEDIISLWDQ SLKPCVKLTP LCVTLHCSDV NI......
F1_FR_MP41
           MWKNNMVDQM HEDIISLWDE SLKPCVKLTP LCVTLNCTKA II......
F2 CM MP25
           MWKNNMVEQM HADIISLWDQ GLQPCVKLTP LCVTLNCSEK IN......
F2KU BE VI
           MWKNNMVEQM HEDIISLWDE SLKPCVKLTP LCVTLNCTEI N...N....
G BE DRCBL
G NG 92NG0
           MWKNNMVEQM QEDIISLWEE SLKPCVKLTP LCITLNCTNV N......
           MWKNNMVEQM HEDIISLWDE SLKPCVKLTP LCVTLNCTDV TNKGNKR.NN
G SE SE616
           MWVNDMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLDCSSV NA.....
H BE VI991
           MWDNDMVEQM QTDIISLWDQ SLKPCVKLTP LCVTLDCSNI TR.....
H BE VI997
           MWENNMVEQM HTDIISLWDQ SLKPCVKLTP LCVTLNCTNV RN......
H CF 90CF0
           MWKNDMVDQM QEDIISVWDE SLKPCVKITP LCVTLNCSDV NSNNS.....
J SE SE702
J_SE_SE7.88 MWKNDMVDQM QEDIISVWDE SLKPCVKITP LCVTLNCSNI TSNSN.....
           MWKNNMVEQM HTDIISLWDE SLKPCVKLTP LCVTLTCTNV TN......
K_CD EQTB1
           MWKNNMVEQM HTDIISLWDE SLKPCVELTP LCVTLNCTDY KG.....
K CM MP535
           MWENKMADQM QEDIISLWEQ SLKPCVKLTP LCVTMLCNDS YGEER.....
N CM YBF30
O CM ANT70
           IWKNYMVEQM QEDIISLWDQ SLKPCVQMTF LCVQMECTN. .....
O_CM_MVP51 IWKNYMVDQM HEDIISLWEQ SLKPCEKMTF LCVQMNCVD. ......
O_SN_99SE_
           IWKNYMVEQM QEDIISLWEQ SLKPCVQMTF LCVQMNCTNY VQ......
           IWENYMVEQM QEDIISLWEQ SLKPCVQMTF LCVQMNCTN. .....
O_SN_99SE
U_CD__83C MWKNKMVEQM HEDIISLWDQ SLKPCVKLTF LCVTLNCIDV KN.....
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	151				200
00BW0762_1	ATNV	N	A	DYKNCSFNIT	ייים אוריים אייים איים אייים א
00BW0768_2	· · · · · · · THE	· v	TNDTLYG	RIKNCSEMM	TETDDVVDVD
00BW0874_2	7	· E	GNTTYGG	EMRNCSFNIT	TEIRDANARE
00BW1471_2	vı	Т	YNNNMTE	BMKNCSFNTT	TEDKDKKKKČE
00BW1616 2	· · · · · YNGTY	s	D	GMKSCSFNIT	TEDEDVICE
00BW1686 8	RDATSSS	E	GMREGMP	BIKNCSFNVT	TELRUKKKKE
00BW1759 3	KT.NFT	' D	TTNG	BIKNCSFNVI	TELRUKRKNV
00BW1773 2	NGS		VTOC	EIKNCSFNVT	TEVRDRKKNE
00BW1783 5	. TNSTAFNTT	` T	K P	EMKNCSFNWT	TELRDKIQKV
00BW1795 6	. TDNTIDEGM	. G	N	EIKNCSFNTT	TEIRDRKRKE
00BW1811 3		т	VMNCTVD	EMKNCSFNIT	TELROKKKRE
00BW1859 5	KN	T	TVD MI	EIKNCSFNTT	TEIRDKKKQV
00BW1880 2	NSNAS	M	FC	EIENCSFNIT	TELRDRKKNV
00BW1921 1	GNGN		DMG	EIKNCSFNIT	TELRDKRKQE
00BW2036 1	TYHNVTV	• • • • • • • • • •	····RIG	ETKNCSFNVT EVKNCSFNMT	TELRDKRQQV
00BW2063 6	MASNTVOVT	· · · · · · · · · · · · · · · · · · ·	UTD	EVKNCSFNMT	TELRDKKQNV
00BW2087 2	MMVTSC	- 	CODMICE.	IMKNCSFNIP	TELRDKSKKE
00BW2127 2	ΝΑΤΑΝΙ	Λ	CINITICE	QMRNCSFNAT	TEÏKDĶĶÕKV
00BW2128 3	KCMCTM	· A. · · · · · · · · · · · · · · · · · ·	THNPMEG	EIKNCSFNAT	TEIKDRKKQV
00BW2276 7	Cu	· · · · · · · · · · · · · · · · · · ·	TSENKEG	EMKNCSFNIT	TELINKKQRE
00BW3819 3	VIII.GI			DMTNCTFNAT	TEIKDKKRKV
00BW3842 8	TVANTOMY	N	TTKNNMD	EIKNCSFNVT	TEVRDKKKQV
00BW3871 3	PNOTION		YNDTMYG	EIKNCSFNMT	TELRDKKEKM
00BW3876 9	KNOTKNON	N	YTYEGIG	EIKNCSFNMT	TELRDKKKNV
00BW3886 8	TOTAL	Т	VNHSMKE	ETKNCSFNAT	TEIRDKKRKV
00BW3891 6	.DIEN		MKE	EMRNCTFNTT	TEIRDKEKOM
00BW3891_6	AT.SNG	T	VTING	EIKNCSFNVT	TELRDKRKNE
	· · · · · · VIINN	v,	TANNNTS	DMKNCSFNAT	TEVTDKIRKE
00BW5031_1.		· · · · · · · · · · · · · · · · · · ·	TVAEMKG	EIKNCSFHIS	TEMRDKRQKE
96BW01B21	· · · · · · · · · · · · · · · · · · ·	D	N YOE	KIKNCSENTT	TETEDVIVOGG
96BW0407	NGTSN	N	SSVPMEE	EMKNCSPNITT	TELDDYKOOG
96BW0502	AINNIM	I	D.NSNKG	EMKNOSEMUT	TEI DDDVOEL
96BW06_J4	GŞNN.ANS	5	YSNDMKE	EIKNCSENMT	TELRDKKOKV
96BW11_06	- NDTLHONLT	D		MKNICSENTITE	TEI DDIOLOUS
96BW1210	N	• • • • • • • • • •	YNNKNNG	ETKNCCEMAT	TETDDYOOM
96BW15B03	.NYSNTMN	S	YNNNTTE	EIKNCTEMMT	TEI DDVVOOU
96BW16_26	SNATMG	N	TLENGGG	EMKNCSRNMT	TETDDVVV
96BW17A09	TN	N	VTSSMTG	CMKNICCENTTO	THE DESCRIPTION
96BWM01_5	. KDINTSNAE	М	K A	EMKNICSENTT	TEI DDEKKOD
96BWM03_2	. NMKKDT		MKE	ETKNOCEROM	THE VOLUME
98BWMC12_2		T	GTNSMNG	OTKNCCPNITT	THE DEVENOR
98BWMC13_4	WILLAUNTID	G	ET. IDK	EMKNCCENTT	TEI DEVICEOR
98BWMC14_a	VDANSTYV	1	HVGNTTT	EMKNCSENMT	TEI DEMINE
98BWM014_1	STRKS.		NPSMOG	DIKNOSENTO	TETADEDDES
98BWM018_d	N	N	DTTYNIE	EMRNCSFNIT	TETEDKEROF
98BWM036_a	· · · · · · · · IV .	T	IDGAMKE	CMKNCSENTT	TEVDDVINICO
98BWM037_d	YTNAT	G	WPTEDE	KIONCSEXTUR	TUIDDVVIIVO
99BW3932_1	AIK	N	GNITMKG	EIKNCSFNAT	TETVUVVVINE
99BW4642_4		N	VNRTMTE	EIKNCSFNIT	MEI DUDNONI
99BW4745_8	TI.TNT	T	IYKYTTS	DIRNCPFNVT	TEI KOKOOKO
99BW4754_7	NTTVT	v		VMKNCSFNVT	TELEDENERSE
99BWMC16 8	• • • • • • • • • • • • • • • • • • • •	N	LNNNMKE	ETKNICSENTE	TELRUKKKQE
A2_CD_97CD	NS		TE	EIKNCSFNIT EIKNCSYNMP	TETKDKKÓWA
A2_CY_94CY	SNSSSTO	S	DTNE	EIKNCSYNTT	TELKDKTQKV
A2D97KR	STOS	• • • • • • • • • • • • • • • • • • • •	DDGM	NTMNCSFETT	TTPKDKJÁKA
A2G_CD_97C	TGNN	S	TETE	EMKNCSYNIT	TEPKDKKÓKA
A_BY_97BL0	NNSSVNS	N	SSDSLEY	XMKNCSFNMT	TETKOKIKIA
A_KE_Q23_A	NTTGDR		DOUBLY	GLKNCSFNMT	TETKDKKKIA
A_SE_SE659	NS. TRV	V	NITTOKE	EIKNCSFNMT	TELKUKRQKV
A_SE_SE725	NG. TON	V	NITH V	GMRNCSFNMT	TETANKÓ Ó Ó A
– –			444 444 . V	GIRNUSFNMT	TETKNKKŐKG

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A_SE_SE753
            ...KNITVSS N..... NNISISNSTE DMRNCSFNMT TELRDKQQKV
 A_SE_SE853
            ....VTNSSHS Y..... NVTNMQ.... EMKNCSFNVT TELRDKRQKV
            ......SSVT N...... ITSDMAG... EIKNCSFNMT TEIRDKRQKV
 A SE SE889
 A SE UGSE8
            ...NTNSTSA N..... LTDSVKG... EMRNCSFNIT TELRDKKKKV
 A UG 92UG0
            ...NITNSIT N..... SSVNMRE... EIKNCSFNMT TELRDKNRKV
 A UG U455
            ...NTN.NNT N..... ITDGVR...E EMKNCSFNMT TELRDKKQKV
 AC IN 2130
            ...NSTGWGK ...... E EIKNCSFNIT TELRDKRQKV
...TVN.... ITDDMKG... EIKNCSFNMT TELRDKKQRV
 AC RW 92RW
 AC SE SE94
            ...TPNNATH N..... DSM..V...G DMKNCPFNMT TELRDKRRKE
 ACD SE SE8
            ...TNATDSN N..... ..ASLQDMAK EMTNCSFNMT TELRDKKQRV
 ACG BE VI1
            ....SNGTAI N..... ITESIKG... EMKNCSFKAT TEIKDKKKKE
 AD SE SE69
            .....ETSMN G...... EIKNCSFNMT TELRDKEQQV
            ...VTNATNI T..... NANTITG... EMKNCSFNMT TELMDKKRKV
 AD SE SE71
            ...HTDTTNN ..... TSIQPSQ PSANCSFNVT TAIRDKQQKV
 ADHK NO 97
 ADK CD MAL
            AGSNRTNAEL KM..... .....EIG EVKNCSFNIT PVGSDKR.QE
 AG BE VI11
            .STREIRGKN CSLD..... TEVG ELKNCSFNIT TELRDKKKTE
' AG NG 92NG
            STGNSAGTNA TCNI..... EEAN NLKNCSFNIT TEIRDKKKTE
 AGHU GA VI
            ...ITNNSTD KANV..... ...TNN..DA EMRNCSFNIT TEIRDRKKKE
            .....NSTES N...... ITAEMQG... EIKNCSYNMT TELRDKQRKI
 AGU_CD Z32
 AJ BW BW21
            .....GCTNN NCT...... ......VS EMKECHFNIT GGGR..RKKE
 B_AU_VH AF
            ...NVTFTNS RHVTNS.... .SYVGSMEKG EMKNCSFNIT TSIRDKRHKE
 B_CN_RL42
            ...NATNTSS T..... MEGG EIKNCSFNIT TSIKTKVK.D
            ...NATNTNN SSWT..... ...MTGEMKG EIKNCSFNIT TSIRDKVQKE
 B_DE_D31_U
            ...NATNSS. ..... WGRMEKG EIQNCSFKVT TNIRDKVQKE
 B DE HAN U
 B FR HXB2_
            ...NDTNTNS SS.G..... ...RMIMEKG EIKNCSFNIS TSIRGKVQKE
 B_GA_OYI
            .LRNATNTTS SS..... ... WETMEKG ELKNCSFNTT TSIRDKMQEO
 B GB CAM1
            ...TRTNSSD WDRR..... ...EGEKMKG EIKNCSFNVT TSIRNKVRKE
            ...NDTNTNN SIME.......GG EMKNCSFNIT TSIRDKMQKE
 B GB GB8 C
            ...NATNTTS TNNTAS.... .GSWGAMR.G EIKNCSFNIT TNIRDKVHKE
 B GB MANC
            .N.SSTSENN TNPTIS.... ..GGEGMGEG EMKNCSFNVT TNIRDKVQKE
 B_KR_WK_AF
 B_NL_3202A
            ...NATNTTS S..S..... ...GVIIEKG EIKNCSFKIN TNMKDKAQIE
 B_TW_TWCYS
            ...TMSKNDS N.........TLTMEKG EIKNCSFNVT TSLRNKVQKE
 B_US_BC_L0
            .TNTTSTNTP SGS..... ...WKKMERG EIKNCSFNVL G...DKKQKA
            ...NGTNLKN GTK..... ..IIGKSMRG EIKNCSFNVT KNIIDKVKKE
 B US DH123
 B US JRCSF
            ...NATNTTS ..... .SSEGMMERG EIKNCSFNIT KSIRDKVQKE
 B_US_MNCG
            ...NTTNTNN STANN.NS.. .NSEGTIKGG EMKNCSFNIT TSIRDKMQKE
B US P896
            ...NITKNTT N....PTS.. .SSWGMMEKG EIKNCSFYIT TSIRNKVKKE
 B US RF M1
            ....GTNVTS SSG..... ...GTMMENG EIKNCSFQVT TSRRDKTQKK
            ...KATNTNS SN..... ...WKEEIKG EIKNCSFNIT TSIRDKIQKE
 B US SF2 K
            LKNETNTNS SSG..... ... GEKMEEG EMKNCSFNVT TLIRNKRKTE
 B US WEAU1
            ...WNATSTS KNTTITNS.. .SNERPMEKG EMKNCSFSIT TSIRDKVQKE
 B_US_WR27
 B_US_YU2_M
            .R.NATNTTS SS..... WETMEKG EIKNCSFNIT TSIRDKVQKE
 BF1_BR_93B
            ...NST.....QND...... ...TLKEEPG AIQNCSFNMT TEVRDKQLKV
 C_BR_92BR0
C_BW_96BW0
            ....IDYN.. N...... RTDNMGG... EIKNCSFNMT TEVRDKREKV
            V...PANGTSN ...... SSVSMKE... EMRNCSFNIT TELRDKNKQE
 C BW 96BW1
            C BW 96BW1
            ....NS..NA T...... YNNKNNG... EIKNCSFNAT TEIRDKQQKV
            .NYSNTMNAT S..... YNNNTTE... EIKNCTFNMT TELRDKKQQV
 C_BW_96BW1
 C ET ETH22
            ..........N N......... SINSAND... EMKNCSFNIT TELRDKKRKA
            ....RNVSSY N...... TYNGSVE... EIKNCSFNAT PEVRDRKQRM
 C IN 93IN1
            ....NDSTHN E..... TYTESVK... EIKNCSFNAT TEIRDRKQTV
 C IN 93IN9
 C_IN_93IN9
            ATNNVNATSN G..... NATSNGE... EIQQCFFNVT TEMRDKKQRV
 C_IN_94IN1
            ....QNGTYN D...... ESNK... EITNCTFNTT TEIRGRKOKV
 C_IN_951N2
            ....GNGTHS K..... TYNESMK... EIKNCSFNAT TVIKDKKQTV
 CRF01 AE C
           .GTAKL....N .......DTIGD EVRNCSFNVT TELRDKKQEV
 CRF01_AB_C
            DRIK..... MED AVRNCSFNMT TELQDKKQEV
 CRF01 AE C
            NTTEK....P E...... ..IEISEMQK EVSNCPFNIT TELRDKEQEV
CRF01 AE T
            I.....TNVP N...........IG..NITD EVRNCSFNMT TEIRDKKQKV
CRF01 AE T
            CRF01 AE T
```

CRF01 AE T	TKADNMTNVS	N	ITIGNITD	EVENICALENIA	MDI TOWARD
CRF01 AE T	KTNVS	N.	IIG.NITD	EAMICTLIMIT	IDTIDKKÖKA
CRF01 AE T	T TRAD	N	IVGTD	EVENCTION	TELTDKKQKV
CRF02 AG F	NSSTSNS	SNSSTDINDT	IDSDMQE	ETWICCENME	TEPKDKLŐŐA
CRF02 AG F	NSSTSVK	S	TERDMOC	EINNCSFNMI	TEURDKKQKV
CRF02 AG G		• • • • • • • • • • • • • • • • • • • •	_	EIKNCSFNMT	
CRF02 AG N	SASA	NT	LTSDMNG	EIKNCSFNMT	TELRDKKQKV
CRF02 AG S	SS GN	м	ISENMQG	EIKNCSFNIT	TEVRDKKKKM
CRF02 AG S	DAINI	• • • • • • • • • •	SKINEVQ	EIRNCSFNMT	
CRF03 AB R	FUTCTNT		SKINEVQ	EMKNCSFNMT	TVLKDKKKKM
CRF03 AB R	MOTETMA	·	GIEMM	EMKNCSFNIT	TDLRDKVKKE
CRF04 Cpx	TOTAL	CMAL	KE	KNCSFNIT	TDLRDKVKKE
CRF04_Cpx_	TATALCTTCALCTC	MCTTV	KE	GIKNCSFDIT	TEIRDKKKKE
	INNSTINSIG	NSTV	KSTA	EIKNCSFNIT	TEVRDKQKKE
CRF04_cpx_	NOTATION	NVII	TN	EMKNCSFNIT	TEIRDKKKKA
CRF05_DF_B	NSTANST	TNST	TLKEETG	AVQNCSFNMT	TEVNDKKLKV
CRF05_DF_B	ATTTSKN	ISATPISN	PNDTLKEEQG	AIQNCTFNIT	TEVKDKNKRV
CRF06_cpx_	STNSTLGNNS	TIVD	DISK	EIKNCSFNIT	TEIRDKTKKE
CRF06_cpx_	T.KNI	TVES	GE	EIKNCSFNVT	TEIRDKQKEE
CRF06_cpx_	NNN	TVEG	KE	EIKNCSFNVT	TEIKDKKKKE
CRF06_cpx_	YSNETVGKSL	TVKD	RE	EIKNCSFNIT	TEVRDQKKTE
CRF11_cpx_	• • • • • • • • • •	• • • • • • • • • •	YNTT	EMKNCSFNVT	TELIDRRKQE
CRF11_cpx_	• • • • • • • • • •	• • • • • • • • •	DNAT	DIKNCTFNIT	TELEDKKKNE
D_CD_84ZR0	TDNNSTLPTV	KP	GE.	.MKNCSFNIT	TVVTDKRKQV
D_CD_ELI_K	MGNNVTTEEK	G		.MKNCSFNVT	TVLKDKKQQV
D_CD_NDK_M	KGNGKVEEEE	к		RKNCSFNVR	DKREQV
D_UG_94UG1	TTNTT	G		.MANCSFNIT	TEIRDKKKOV
F1_BE_VI85	\dots NSQ \dots		EKPG	AMONCSFNMT	TEVRDKKLKL
F1_BR_93BR	NGTNDTI	AIND	TLKEDPE	AIONCSFNTT	TEIRDKOLKV
F1_FT_FTN9	TNDTLS.	DQSS	TLKEEPG	AIQNCSFNMT	TEVEDKKOKV
F1_FR_MP41	TSNATTT	NDTS	TP.EESG	AIQNCSFNMT	TEVKDKKLRV
F2_CM_MP25		TTLA	PNVTISE	EMKNCSFNIT	TEIRDKOKKE
F2KU_BE_VI	INSTDLT	NWANKTNNWA	NETTLLNITT	GMRNCSFNIT	TMLKDKKKKO
G_BE_DRCBL	NS	TRNI		RMTNCSFNMT	
G_NG_92NG0	. SANHTEANN	TV	ENKE	EIKNCSFKIT	TERGGKKKEE
G_SE_SE616	STDNSTETNN	S.TV	DNPG		TEIRDKKKKE
H_BE_VI991	TNVTKSN	NSTD	INTGEIQ		TAIRDKNOKV
H_BE_VI997	NDTNSSS	TVNA	TSSPSAN		TVIRDKQQRV
H_CF_90CF0	NTSNSTS	SMEA	GG		TVLRDKOOKV
J_SE_SE702	TDSNS	SASN	NSPE		TEIRNKRKOE
J_SE_SE788			SPD		TEIRNKRKOE
K CD EQTB1		NDT	NINATVTSTD		TELKOKKKRV
K CM MP535	TNSTN		NATSTVVSPA		TEIKDKKKKE
N CM YBF30			EPDIGYK		TELTDKKKOV
O_CM_ANT70	IAG		TTNEN		TVIKDKKEKK
O_CM_MVP51			LLNETIN	EMRNCSENUT	TVLTDKKECK
O SN 99SE			INNDTSSPEN		TVVKDKKEKK
O SN 99SE			VKNDTSSEN	LMKKCEENUA	TVLKDKKEKO
U CD 83C	STNN	N	TEEA	TTTNCCERVI	TATIVEVEVE
			·····IDDA	TTINCOLKVP	TUNDALEIV

60458026 032803

	201				250
00BW0762 1	YALFYRLDIV	QLGE	NNAN	SE	230 VDT.T
00BW0768_2	HALFYRLDIV	PLDEKDK		SN	VPLT
00BW0874_2	SALFYRLDIV	PLNGS	ERNK	SE	VRLT
00BW1471_2	RALFYRLDIV	PLNESDN	NSY	RE	YRLT
00BW1616_2	YAIFHSLDIV	PLEN		SE	······································
00BW1686_8	YALFYKLDIV	PLEE	NDI	ST	YRT.T
00BW1759_3	HALFYRLDIV	PLEGE	NNTN	NE	YRLT
00BW1773_2	HALFYRLDIV	QLD	N	SS	YRIJT
00BW1783_5	YALFYKLDIV	PLEGNNS	E		VRI.T
00BW1795_6	YALFYRLDIV	SLDNENN	KT.	AE	YRI _I T
00BW1811_3	YALFYKPDIV	PLDGS	NS	SE	YRLT
00BW1859_5	YALFYKIDIV	PLNDN.	NSN.N	SM	VDT.T
00BW1880_2	YALFYRLDVV	PLDSPS	NATN	SR	VPLT
00BW1921_1	YALFYRLDVV	QLN		SE	VPI.T
00BW2036_1	YALFYKLDIV	PLNGNSG		SE	VDI.T
00BW2063 6	YALFYKLDIV	PLGNTNG	T	E	VDI.T
00BW2087 2	YALFYKLDIV	SLDD	NN	S	VDI.T
00BW2127 2	YALFYRLDVV	PLDND	SA	TN	VDIT
00BW2128 3	YALFYKLDIV	PLNNS	SDNSS	GE	VDI.T
00BW2276 7	QALFYKLDIV	PLNSTGE	NNN	TR.	VDT.T
00BW3819 3	YALFYRLDVV	PLNGK	NS.	55	VDIT
00BW3842 8	HALFYRLDIV	PLEDNSG	NSS	SN	VDIT
00BW3871 3	YALFYKLDIV	PLND	N N	NE	VDIT
00BW3876 9	NALFYKLDVV	PLHE	GM	Q	VDIT
00BW3886 8	YALFYRLDIV	PLHDSSS	DG	SE SE	VIII
00BW3891 6	HALFYRLDIV	PLNG	KNIOS	NF	VDIT
00BW3970 2	NALFYTLDIV	PLDENQ		M	VDIT
00BW5031 1	FALFNILDIV	PLNNEN	אידינאי	en	VDIT
96BW01B21	YALFYKFDVV	PLN	GNNT	SD	IKLI
96BW0407	RALFYSLDIV	QPNN	C	TE	VDIT
96BW0502	HALFYRLDVV	PLQG	MINI	NE	VDIT
96BW06 J4	YALFYRLDVV	PLGD	N	55	VDIT
96BW11 06	YALFYRLDIV	PLNNKNE	S	SE	VDIT
96BW1210	YALFYRLDIV	PLDN	NS	SE	VDIT
96BW15B03	YALFYKLDIV	PLNSNS		SE	VDIT
96BW16 26	YALFYRLDVV	PLNGE	NSNSS	GE	VDI.T
96BW17A09	SALFYRLDIV	PLNENNS	SSN	SE.	VDI.T
96BWM01_5	YALFYKLDIV	PLTNDAS	EN.	SE	VDI.T
96BWM03 2	YALFYKLDIV	PLDGNNE	DGN	КО	VDWT
98BWMC12_2	SALFYRLDIV	PLK	ENS	SE	. VPT.T
98BWMC13_4	QALFYRLDIV	PLDNANG	T	SE	. VDI.T
98BWMC14_a	YALFYRLDIV	PLGE	D	SS	VPLT
98BWM014 1	YALFYKLDIV	ELDG	NS	SN	VVI.T
98BWM018_d	SALFYKLDIV	PLD	NSS	SK	VILI
98BWM036_a	YVLFYKLDIV	PLNGNG	SN	SE	VDI.T
98BWM037 d	YALFYRPDIV	PLNEG		N	VDI.T
99BW3932_1	YALFYRLDIV	PLKN		SE	VDI.T
99BW4642 4	NALFYKLDIV	PLNEK.	ANNSY	SY	VDI.T
99BW4745 8	YALFYRIDIV	PLDE	NNNS	SE	VDIT
99BW4754 ⁷ 7	HALFYRLDIV	PLETK	NSNR	SA	VDI.T
99BWMC16_8	YALFYKVVIV	PLSE	NST	SR	VDI.T
A2_CD_97CD	YSLFYELDVV	LLNRSKN	SSY	ST	VDI.T
A2_CY_94CY	YSLFYRLDVV	QLDESENKNT	SGSN	TL	TUNE
A2D 97KR	QALFYELDIV	QLNSSDSND.	TI.NI	RO	TUNI
A2G CD 97C	RSLFYTLDIV	QINKDNN		.т.	VDI.T
A BY 97BLO	HSLFYKLDIV	STSNNDSX		.Q	VDI.T
A KE Q23 A		PINEN	.OG	SE	TUNI
A SE SE659	HSLFYRLDIV	QMNEN	RGNSSNSSV	NE	VDIT
A SE SE725	YSLFYKLDIV	QINDN	GNNSNNS	QF	VDIT
 :					IKDI

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A_SE_SE753	YSLFYRLDLV	KIDEN	.KSNSSN	sk	YRLT
A_SE_SE853	TSLFYKLDVV	PIGGN	DTNS	TQ	YRI.T
A_SE_SE889	HALFYRLDVV	PMDN	NNS	. T	VDIT
A_SE_UGSE8	YSLFYKLDIV	KINKNKSFRG	. KNSSGNSSS	DR	VDIT
A_UG_92UG0	YSLFYKLDVV	QINNG	NNSS	NL	YRLT
A_UG_U455_		QINKTD		NS	····YRLI
AC_IN_2130		PIEEGQGNS.		KE	YRLI
AC_RW_92RW		QINSNSN		NQ	
AC_SE_SE94	HALFYRLDIV	PLDEGNSNSN		SD	YRLI
ACD_SE_SE8	YSLFYKLDVV	QINSN		sq	····YRLI
ACG_BE_VI1		PLNKENK		GK	YRLI
AD_SE_SE69		QMGNSNS		SQ	····YRLI
AD_SE_SE71		QINENQ		KE	YRLI
ADHK_NO_97		SIDN		TQ	YRLI
ADK_CD_MAL		QIDDSDN		s	YRLI
AG_BE_VI11		PINNDN		• • • • • • • • • • • • • • • • • • • •	SSYMLI
AG_NG_92NG		PIDGNNNV		.s	NNYRLI
AGHU_GA_VI	YALFYKHDLV	PITN		KT	FILI
AGU_CD_Z32		PIEENSSNG.		SE	····YRLI
AJ_BW_BW21	AAPLAKEDIA	LIKDRPN		NY	SEYILV
B_AU_VH_AF		QIDGS		TS	····YRLI
B_CN_RL42_ B_DE_D31 U	VALIDVICTORY	PIGND		TS	····YRLI
B DE HAN U		PIDND		TS	YRLI
B FR HXB2		PIDNNKTS PIDND	NRDNT	TS	YMLI
B_GA_OYI	INTERNATION	PIDKN		TS	·····YKLT
B CB CAM1	TARLIVIDAD	PIDKAN		TK	FRLI
B GB GB8 C	TADE I KDDAA	SIGSD	• • • • • • • • •	TS	YTLI
B_GB_MANC	VALEVET DULV	PIBKK		TS	YILT
B KR WK AF	VALEVEL DIT	PIDN		TS	FRLI
B NL 3202A	VALEVKLDIN	DIDNE N		TS	····.YALR
B_TW_TWCYS	VASEVDINIA	OTDEN	TNTSY	TS	YRLI
B_US_BC LO	YALFYKLDIV	DIDNIDEN	s	TS	YRLI
B US DH123	YAI.FYPHDW	DIDDNI	I	TK	YRLI
B US JRCSF	YALFYKI.DVV	DID	NKNN	TS	YRLI
B_US_MNCG	YALLYKLDIV	SIDND		TK	YRLI
B US P896	YALFNELDVV	DIE	NTNN	TS	YRLI
B_US_RF_M1	YALFYKI.DVV	DIEKCHICDE	N.NTSNNTSY	TK	YRLI
B_US_SF2_K	NALFRNLDVV	DIDN VC	TTTNY	GN	YTLI
B US WEAU1	YALFYKLDVM	PIDHONTS	··········	TN	YRLI
B US WR27	HALFYRLDVV	PTDK	NNTN		YTLI
B US YU2 M	YALFYNLDVV	PINN		A.C.	
BF1 BR 93B	HALFYRLDIV	PISNONSSNO	NCC	AS	YRLI
C BR 92BR0	HALFYRLDIV	PLKNE	SSNTS	RE	·r····YRLI
C BW 96BW0			····SNS	GD	VRI.I
C BW 96BW1	YALFYRLDIV	PLNNKNR	SN.	NE	·····YRLI
C_BW 96BW1	YALFYRLDIV	PLDN	NS	CP.	·····YRLI
C_BW 96BW1	YALFYKLDIV	PLNSNS		SE	YRLI
C ET ETH22	YALFYKLDIV		NGS	TO TE	YRL1
C IN 93IN1	YALFYGLDIV		CCDMC	ID	YRLI
C IN 93IN9	YALFYRLDIV		KANICC	SE	·····YRL1
C IN 93IN9	HALFYRLDLV	PLDNENKSS.	PONCE	KT	·····YRLI
C_IN_94IN1	YALFYKLDIV		NQS	************	YKLI
C_IN_95IN2	YALFYKLDIV		Dence	GY	
CRF01 AE C	HALFYVPDIV		. NKNggang	SE	YKLI
CRF01_AE_C			NSNTSGQNNS	ык ЭБ	YILI
CRF01_AE_C	YALFYRSDLV	PIB	RNSGENNG	99	FRLL
CRF01_AE_T	HALFYKLDIV	OIEDK	NDS	CK	YKLI
CRF01_AE_T	HALFYKLDIV	OMN	·····KNS	OR	VDI -
CRF01_AE_T	YALFYKLDIR	OMN	·····SNS	SE	IKUL
				·····	

SD458D26.0328UE

CRF01 AE T	YALFYKLDTI	PIG	MATAY	NM .	110.00
CRF01 AE T	HALFYKLDTV	QIEDK		OF	·····YRLI
CRF01 AE T	OALFYKLDIV	QMGG	Moc	OE	·····YRLI
CRF02 AG F	SALFYRLDVV	QINES	CM	50	·····YRLI
CRF02 AG F	SALFYRLDVV	QINES	CM	SQ	·····YRLI
CRF02 AG G		QMNNS		.Q	······YRLI
CRF02_AG_N		QINEN		SQ	·····YRLL
CRF02 AG S		QINETG	NG	IQ	YRLI
CRF02 AG S	AALFYKIDIV	PIDKN	DIN	TQ	·····YRLI
CRF03 AB R	YALFYKLDVV	QIDND	A	11	·····YRLI
CRF03 AB R		QIDND		.s	·····YRLI
CRF04 cpx	YALFYRIDIV	PINARVPING	CATDAINGE	.5	·····YRLI
CRF04_cpx_	HALFYRLDVV	PINNNVPINN	SINKININS I	EE	·····YMLI
CRF04_cpx_	VALEVELDIV	PINDNNSTN.	CODCOM	RE	····YRLM
CRF05 DF B		PISSDD	SKKSSNT	SD	YMLI
CRF05_DF B	HAI.FVDI.DIV	SINS	SSN	55	····YRLI
CRF06_cpx_		PIGDD	SRK	E	YRLI
CRF06 cpx		PINDG	S	NN	SDYRLI
CRF06 Cpx		PINDN		ŃN	NSYRLI
CRF06_cpx_		QVDG	· · · · · · · · · · · · · · · · · · ·	NN	STYRLI
CRF11_cpx_		PINDNNN	K	NS	STYRLI
CRF11 cpx		PINDS		NV	SDYRLI
D CD 84ZRO		QIDNEGKNE.	TYPOTY	NI	GQYRLI
D CD ELI K		PIDNDSS	INDITY	GT	····YRLI
D CD NDK M		PIDNDSS		TN	·····YRLI
D UG 94UG1	UNITER KITOM	KINDNDS	TNS	TN	····YRLI
F1_BE_V185	QADI IRDVV	PIGNNN.	N	TS	YRLI
F1 BR 93BR	HAI.FVKI.DIV	QINKDDN.		SE	·····YRLI
F1 FI FIN9	HALFYRLDIE	DICAM N		RT	YRLI
F1 FR MP41	MALEVELDIE	PINNS	SR	BE	YRLI
F2 CM MP25	YALFYKLDVV	OTANIC		SD	YRLI
F2KU BE VI			• • • • • • • • • • • • • • • • • • • •	NTS	YRLI
G BE DRCBL	VALEVEDIA VALEVEDIA	PINEMNNENN	·····NSN	SKKNNNTSNN	SIENSKYRLI
G NG 92NG0	VALEVELDIN	PISNGN		NS	TWYRLT
G SE SE616	VAPPVDIDIN	PINN	• • • • • • • • • •	.K	•
H BE V1991	HALPVOADTV	QIDEGER		.A	
H BE VI997	HAI.FYDI.DVV	PIDETSNNN.	NKSD	NH	
H CF 90CF0	HALFYRLDVV				
J SB SE702	YALFYRQDVV			TQ	
J SE SE788	YALFYRQDVV	PIN	· · · · · · · · · · · · · · · · · ·	DN	
K_CD_EQTB1	SALFYKLDIV			NN	· · · · · · · · · · · · · · · · · · ·
K CM MP535	SALEVELDIA.	PLN. GEGNNS	· · · · · · ESE	• • • • • • • • • •	
N_CM_YBF30	VSI.FVVFDVV	PINAYN	· · · · · · · · STE	• • • • • • • • • •	
O CM ANT70	OALEVVEDI.M	EI METECTAL			
O CM MVP51	OVI'EAMBUL'S	ELNETSSTNK KVNDSNAVN.	Т	NS	KMYTLT
O_SN_99SE_	OVIEAN MILITARY	KINEANDT	• • • • • • • • • • • • • • • • • • • •	.G	TTYMLT
0_SN_99SE_	ONIFYNCHIM	KAMEMMUI	• • • • • • • • • • • • • • • • • • • •	.к	DMYTLT
U_CD 83C	ATTLIASTIN	KVNENND	• • • • • • • • • • • • • • • • • • • •		TMYTLI
~_cr	TITHETENO	PLNVTN	N	55	ISSTYRLI

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00BW0762_1 NCNTSTITQA CPKVNFDPIP IHYCAPAGYA ILKCNTKTFD GTGPCTNVST
            NCNTSAVTQA CPKVSFEPIP IHYCAPAGYA ILKCNNKTFN GTGPCHNVST
 00BW0768_2
            NCNTSAITQA CPKVSFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCNNVST
 00BW0874 2
            NCNTSTITQA CPKVTFDPIP IHYCAPAGYA ILKCNNETFN GTGPCNNVST
00BW1471 2
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00BW1616_2
00BW1686_8 NCNTSSISQA CPKVSFGPIP IHYCAPAGYA ILKCNNKTFN GTGPCQNVST
           NCNTSAVTQA CPKVTFDPIP VHYCAPAGYA ILKCNNKTFN GAGPCNNVST
00BW1759_3
00BW1773_2 NCNTSAITQA CPKVSFDPIP IHYCTPAGYA ILKCNNQTFN GTGPCNDVSS
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00BW1880_2 NCNTSAITQA CPKINFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCNNVST
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00BW2063 6
00BW2087_2 NCNTSAITQA CPKVSFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCNNVSI
00BW2127_2 NCNTSAITOA CPKISFDPIP IHYCAPTGYA ILKCNNKTFN GTGPCNNVST
00BW2128_3 NGNTSALTQA CPKVSFDPIP IHYCTPAGYA ILKCNNKTFN GTGPCNNVST
00BW2276_7 NCNTSAITQA CPKITFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCQNVSP
00BW3819_3 NCNTSAVTQS CPKISFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCNNVST
00BW3842_8 NCNTSAITQA CPKVSFDPIP IHYCAPAGYA IIKCNNKTFN GIGPCQNISI
           NCNTSAISQA CPKVSFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCQNVST
00BW3871_3
00BW3876_9 HCNTSTITQA CPKVSFEPIP IHYCAPAGYA ILKCNDKTFS GTGPCLNVST
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00BW3891_6 NCNTSAITQA CPKVSFDPIP IHYCAPAGYA ILKCNNKTFN GTGPCNNVST
00BW3970_2 NCNTSKVTQA CPKVSFDPIP LHYCAPAGYA ILKCNNNTFN GTGPCNNVST
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AGHU GA VI
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AGU CD Z32
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B DE D31 U
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B DE HAN U
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B_FR_HXB2
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B_GA_OYI
            VQCTHGIRPV VSTQLLLNCS LA.EKEVVIR SENFTNNAKT IIVQLKEPVE
B GB CAM1
B_GB_GB8_C VQCTHGIRPV VSTQLLLNGS LA.EEKVVIR SDNFTDNVKT IIVQLKEAVE
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B_KR_WK AF
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B_TW_TWCYS
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B_US_BC LO
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B US DH123
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B US JRCSF
B_US_MNCG_
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B US P896
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B US RF M1
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BF1 BR 93B
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CRF01_AE_T VQCTHGIKPV VSTQLLLNGS LAEE.KIIIR SENLTNNAKT IIVHLHESVB
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CRF02 AG N
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D CD NDK M
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N_CM_YBF30
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O_CM ANT70
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O CM MVP51
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  A UG 92UG0
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 B DE HAN U
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C_IN_93IN1 IVCTRPNNN. TRKSIRIG. PGQTFYATG ... DIIGD IRQAHCNISE
C_IN_93IN9 IVCTRPNNN. .TRKSIRIG. .PGQTFYATG ....BIIGD IRQAHCNISK
C_IN_93IN9 IECVRPNNN. .TRESIRIG. .PGQTFYATG ..... EIIGD IRQAHCNISA
C_IN_94IN1 IVCTRPNNN. .TRKSIRIG. .PGQTFYATG ..... BIVGN IRQAHCNISK
                        IMCTRPDNN. .TRKSIRIG. .PGQTFYATG .....DIIGD IRQAHCNISE
C_IN_95IN2
                        INCTRPFKN. : MRTSARIG. . PGQVFYKTG ..... SITGD IRKAYCEING
CRF01_AE C
CRF01 AE C
                        INCTRPPKK. .VRISARIG. .PGRVFHTTG .....NINGD IRKAYCEINK
                        INCTRPFKK. .MRTSVRIG. .PGRVFYKTG ...SITGD IRKAYCEING INCTRPSNN. .MRTSMRIG. .PGQVFYRTG ...SITGD IRKAYCEING INCTRPSNN. .TRTSITMG. .PGQVFYRTG ...DIIGD IRKAYCEING
CRF01 AE C
CRF01 AE T
CRF01 AE T
CRF01_AE_T INCTRPPYN. .KRTRTSIG. .QGRVLYRTG .....DITGN IGKPYCEING
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CRF01_AE_T
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 CRF01_AE_T
               INCTRPSNN. .TRTSITIG. .PGRVFYRTG .....DIIGN IRKAYCBING
               INCTRP.TI. .YKKKTTMG. .PARVYHRTG .....DVIGD IRKAYCQING
CRF01 AE T
CRF02 AG F
               INCPRPNNN. .TRKSVRIG. .PGQTFYATG ....DIIGD IRQAHCNVSR
              INCTRPNNN. TRKSVRIG. PGQTFYATG ...DIIGD IRKAHCNVSR
INCTRPNNN. TRKSVRIG. PGQTFYATG ...GIIGD IRQAHCNVSR
INCTRPNNN. TRKGVHIG. PGQAFYATG ...DIIGD IRQAHCNVSK
INCTRPGNN. TRKSVRIG. PGQTFYATG ...DIIGD IRQAHCNVSW
CRF02 AG F
CRF02 AG G
CRF02 AG N
CRF02 AG S
CRF02_AG_S
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CRF03 AB R
              INCTRPNNNT .RK.GIHIG. .PGRAFYATG DIT..G...D IRQAHCNISI
              INCTRPNNNT .RK.GIHIG. .PGRAFYATG DII..G...D IRQAYCNISR
CRF03 AB R
CRF04_cpx_
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              INCTGLNNNT GGSERIGIG. .PGHTWYATG NIV..G...D IRQAHCNISG
CRF04_cpx_
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CRF04 cpx
CRF05 DF B
              INCTRPNNNT RKS..IHLG. .PGQAFYATG DII..G...D IRKAHCNVSR
CRF05 DF B
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CRF11_cpx_
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CRF11_cpx_
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              INCTRPYKKE .RQ.RTPIG. .OGQALYTTR YT.....TRI IGQAYCNISG
D CD 84ZR0
D CD ELI K
              ITCARPYQNT .RQ.RTPIG. .LGQSLYTTR SR.....SI IGQAHCNISR
D_CD_NDK_M
              INCTRPYKYT .RQ.RTSIG. .LRQSLYTIT GKK..KKTGY IGQAHCKISR INCIRPYNNT .RQ.STRIG. .PGQALFTTK VIG.....D IRQAHCNISG
D UG 94UG1
F1_BE_VI85 INCTRPNNNT RKG..IHLG. .PGQTFYATG AII..G...D IRKAHCNISG F1_BR_93BR INCTRPNNNT RKR..ISLG. .PGRVFYTTG EII..G...D IRKAHCNVSG
             INCTRPNNNT RKS..IRIG. .PGQSFYATG EII..G...D IRKAHCNISG
F1_FI_FIN9
F1_FR_MP41
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F2_CM_MP25
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              IVCIRPGNNT RKS..IRIG. .PGQTFYATG DII..G...D IRQAHCNITG
F2KU BE VI
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G BE DRCBL
              INCIRPNNNT RKSIPIGPG. ...QAFYATG DII..GD... IRQAHCNVSR
G NG 92NG0
G SE SE616
              INCTRPNNNT MKRIRMGIGP ...GQTFYATG AII...GD... IRQAHCNVTK
H_BE_VI991
              INCTRTGNNT RKS..IRIG. .PGQAFYATG DII..G...D IRRAYCNISG
H BE VI997
              ITCTRPNNNT RKG..IHFG. .PGQAFYATG DII..G...N IRQAHCNVSE ITCTRPNNNT RTS..IHLG. .PGRAFYATG DII..G...D IRQAHCNISR
H CF 90CF0
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J SE SE702
J_SE_SE788
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K CM MP535
              INCTRPNNNT RKS..IHMG. .PGKAFYTTG DII..G...D IRQAHCNISG
              INCTRPGNN. .TGGQVQIG. .PAMTFYNIE K....IVGD IRQAYCNVSK
N CM YBF30
O CM ANT70
              MTCERP.QI. .DIQEMRIG. ..PMAWYSMG IGG..TAGNS SRAAYCKYNA
O CM MVP51
             MTCIREGIA. .EVQDIYTG. ..PMRWRSMT LKRSNNTSPR SRVAYCTYNK
O_SN_99SE_ MTCVRQGNQ. .SVQEIQIG. ..PMAWYSMS LAQE.GKPNN SRIAYCKYNI
O_SN_99SE_ MTCERPGNQ. .TVQKILTG. ..PVAWYSMG LKN. .NLTN SRAASCKYNS
U_CD___83C INCTRPGSDK KIRQSIRIG. .PGKVFYAKG ......GI TGQAHCNITD
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A KE Q23 A
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A SE SE725
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 A SE SE889
 A SE UGSE8
 A UG 92UG0
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 AC_SE_SE94 TKWNKTLHKV VTQLRKYFVN ....KPIIFT. .PSSGGDVEV TTHSFNCRGE
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 ADHK_NO 97
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 ADK_CD_MAL
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 AGHU_GA_VI EQWNRTLERV KEKLGRHFK. ..NKTITFKP .AS.GGDPEV TMHIFNCRGE
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C_BW_96BW0 RDWNDTLNRV SKKLAEHFPN ...KTIEFK. .PSSGGDLEI TTHSFNCRGE
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CRF01 AE C
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CRF01 AE T
CRF01 AE T
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F1 BE VI85
            TOWNNTLEYV KAELKSHFPN N..TAIKFNQ .SS.GGDLEI TMHSFNCRGE
F1_BR_93BR TOWRNTLAKV KAKLGSYFPN ...ATIKFNS .SS.GGDLEI TRHNFNCMGE
F1_F1_F1N9 EQWNKTLDRV KAELKLHFNK ....TIQFNS .SS.GGDLEI TMHSFNCRGE
F1_FR_MP41 TQWSKTKTQV QEKLRALFNK ....TIKFNQ .SS.GGDLEI TMHSFNCRGE
F2 CM MP25 KQWYDTLIKI ATEFKDQYN. ...KTVGFQP .SA.CCDLEI TTHSFNCRGE
F2KU_BE_VI ENWNKTLEGV KAKLHGFFTN ...KTIIFKP .HS.GGDPEV VMHTFNCGGE
G_BE_DRCBL TKWNETLRDV QAKLQEYFIN ...KSIEFNS .SS.GGDLEI TTHSFNCGGE
G NG 92NG0
            IKWREMLKNV TAQLRKIYN. ..NKNITFNS .SA.GGDLEI TTHSFNCRGE
            RKWKEALQNV AAELGKIFNK S.SENITFNS .SA.GGDLEI TTHSFICRGE
G SE SE616
H_BE_V1991
            KQWNETLHKV ITKLGSYFD. ..NKTIILQP .PA.GGDIEI ITHSFNCGGE
H BE VI997
            EKWNKTLQQI ATQLSKYFV. ..NRTLIFKP .HS.GGDLEV TTHSFNCRGE
H CF 90CF0
            TDWNKTLHQV VTQLGIHLN. ..NRTISFKP .NS.GGDMEV RTHSFNCRGE
J SE SE702
            KDWNNTLRRV AKKLREHFN. ...KTIDFTS .PS.GGDIEI TTHSFNCGGE
J SE SE788
            RDWSNTLRRV ATKLREHFN. ...KTINFTS .PS.GGDIEI VTHSFNCGGE
           GQWNKTVNQV KKELGKHFN. ...KTIIFQP .SS.GGDPQV TRHIFNCRGE
K CD EQTB1
K_CM_MP535
            EKWNMTLSRV KEKLKEHFKN ...GTITFKP .PNPGGDPEI LTHMFNCAGE
N_CM_YBF30
            ELWEPMWNRT REEIKKILGK ...NNITFRA RERNEGDLEV THLMFNCRGE
O CM ANT70
            TDWGKILKQT AERYLELVNN TGSINMTFN. . HSSGGDLEV THLHFNCHGE
            TVWENALQQT AIRYLNLVNQ TENVTIIFS. .RTSGGDAEV SHLHFNCHGE
O CM MVP51
O_SN_99SE_
            SDWEKALKQT AERYLDLRNN TNTVNITFE. .RSIGGDSEV THLHFNCHGE
            SVWEEALKQT AERYLELMNN TNTVNITFN. .HSTGGDPEV THLHFNCHGE
O SN 99SE
U_CD___83C GEWRNTLQQV AIALRRQFNN ...KSIIFN. .SSSGGDIEI TTHTFNCGGE
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451
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           FFYCNTTRLF NGTYN..... STGD TNS.....TN STITLQCRIK
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           FFYCDTSNLF NKTRR......DN.......AN ETITLPCRIK
00BW0768 2
           FFYCNTSRLF NSTYN..... PNST YIEGR...SN ATITLQCRIK
00BW0874 2
00BW1471 2
           FFYCYTTKLF NSTYN..... STYT GSESN..... ..ITIPCRIK
00BW1616_2 FFYCNTSKLF NGTYN......SNNN TA........DITLQCRIK
00BW1686_8 FFYCNTSNLS NETYL..... ANLT SNVTK....N ATITLPCRIK
00BW1759_3 FFYCNTSNLF NNTYR..... ADNN ITNDNSN.....ITLQCRIK
00BW1773_2 FFYCNTSALF NSTYN.....STNT SGHN...DT RIITLPCRIK
00BW1783_5 FFYCNTSKLF NGTYN.....GTS...ISS...N SSITLQCRIK
00BW1795_6 FFYCNTSELF NGTYN......STG....DSN...S NLITLQCRIK
00BW1811_3
          FFYCNTSOLF NGTYM..... PNTY MS....SSDN RNITTPCRIK
           FFYCNTTHLF NGNG..... ESD INITLPCRIK
00BW1859 5
           FFYCDTTKLF NGTYN..... STEQ TN..... STITLQCRIK
00BW1880_2
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00BW1921 1
00BW2036 1
          FFYCDTSKLF NSSYN..... DTEL YSYNS....T ANITLPCRLK
          FFYCNTSQLF NSSYS.... RHN. ...NTS...N STITLPCNIK
00BW2063 6
          FFYCNTSGLF N..........GTF NGT...HSTN TNITLPCRIK
00BW2087 2
00BW2127_2 FFYCNTTILF NSTYY..... P... NTK...SDTT ETITLPCRIK
00BW2128_3 FFYCNTSLLF DETQL.....SKE.....N NTINIQCRIK
00BW2276_7
          FFYCNTSKLF NGTYM..... PNYN TSN...SSNN SNITLPCRIK
00BW3819<u>3</u>
          FFYCNTSGLF NGTYN......G... TND...NDTD SDITLPCKIK
           FFYCNTSLLF NSSYN..... GNSS YNDTGS...N STITLQCRIK
00BW3842 8
           FFYCNTSILF NDTYW..... FNGT ANDTG....S NNITIPCRIK
00BW3871 3
00BW3876_9
           FFYCNTSGLF NNNLI......NNG. .....AE DTIRLPCRIK
00BW3886 8
           FFYCNTSKLF NSTNN..... NTE. ..SES....N ATITLPCRIK
          FFYCNISRLF NRPNM.... TKNM TSDIKNN... STITLPCRIK
00BW3891_6
00BW3970_2 FFYCNTSSLF NNTYR..... PTYW PGTE....SN STITLQCRIK
00BW5031_1 FFYCNTSQLF NSTYR..... ANTS NS...... NITLPCRIK
 96BW01B21 FFYCDTSELF NSTYM.....SNGG NISS.....S TIIMLPCRIE
  96BW0407 FFYCNTSRLF NESYN.......FDES YWN.N...TN KTIMLPCRIK
  96BW0502 FFYCDTSQLF NSTYS..... PSNG TENK....LN GTITITCRIK
          FFYCNTSRLF DETYL..... GTDED....N GTITLPCKIK
 96BWQ6 J4
          FFYCNTSKLF NSTYI......QLN. .STETP...N STITLPCRIK
 96BW11 06
          FFYCNTSQLF NSTYN..... Y MPS...NNTG TNITLQCRIK
  96BW1210
 96BW15B03
          FFYCNSSKLL NSSYN..... GTSY RGTESN...S SIITLPCRIK
          FFYCNTSKLF NSTYN.....STDR SNN.....T DNITIQCRIK
 96BW16 26
          FFYCNTSILF NSTYN..... STYT GSDSNS.... .TITIPCRIK
 96BW17A09
          FIYCNTSKLF NGTYN.....STG. ....TS...N STITLSCRIK
 96BWM01 5
          FFYCNTSELF NGTYN..... GTD. ..NNS....N KTITLLCRIK
 96BWMO3 2
98BWMC12_2
          PFYCNTSGLF NSTYN..... PNST YTESK...AN SNITLHCRIK
98BWMC13 4
          FFYCNTTKLF NGTYS..... QPN. STGTP...H SNITLPCKIK
98BWMC14_a
          FFYCNTSQLF NSTYN.....G... RNSTT....N ATITLPCRIK
98BWM014_1
          FFYCNTSKLF NSTYN..... ATY NST...DTSN STITIPCRIK
          FFYCNTSGLF NS..... AFNDN...SG GTITLQCRIE
98BWM018 d
          FFYCNTSGLF NSTYY..... SNKT SSN...MTTN EIITIPCKIK
98BWMO36_a
98BWMO37_d FFYCNTSKLF NTSWL......DSYI SNTG....NN SIITLPCRIK
99BW3932_1 FFYCNTSRLF NSTYN..... P... NTK...SNTG SWIILPCRIK
99BW4642_4 FFYCNTSKLF TYQSN..... TY......VAN STITLPCKIK
99BW4745_8 FFYCNTSELF NSTYN..... ANTY NTATGNNS.. TTIILPCRIK
99BW4754_7 FFYCNTSKLF NSTFN..... SNGH DST.....GN DPLTIPCRIK
99BWMC16_8 FFYCNTSNLF NNTYY...........PNMT NTDTK...SN LTITLPCRIK
A2_CD_97CD FFYCNTTGLF NSTWEN.....GTNK QNYTE...SN DTITLQCRIK
A2_CY_94CY FFYCNTTGLF NGTWWNN.......GTWN GPYTPNN.TN GSIILPCRIK
A2D 97KR FFYCDTSGLF NSTWPAN... ASRE NEEKD...R. NVTLPCRIK
A2G CD 97C
          FFYCNTTNLF NSTFNTT... .....SLFN STGRNGTNDN TTITIPCRIK
A_BY_97BL0 FFYCNTTDLF NSTX......DGTVT NSTKAN.... GTITLPCRIK
A_KE_Q23_A FFYCNTSGLF NSTWY..... VNSTW NDTDSTQESN DTITLPCRIK
A SE SE659
          PFYCNTSSLF NSTWS..... NDNNT QGSNSTET.K GTITLPCRIK
A_SE_SE725 FFYCNTSGLF NSTWS..... Q.NDT GVSNSTES.N DTIILPCRIK
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FFYCNTSGLF NSTIL..... NSTKM NDNASRESYD DTITLQCRIK
 A SE SE753
            FFYCNTSGLF NSTWS..... SNASE PMSNSTES.N DTITLQCRIR
 A SE SE853
            FFYCNTSGLF NSTWN..... GTDSM QKLNST.... GNITLPCRIK
A SE SE889
            FFYCNTSGLF NSSWN..... END.T KVNYNTES.N DTITLQCRIK
A SE UGSE8
            FFYCNTSGLF NSTWV..... NGTTS STSN..... GTITLPCRIK
A UG 92UG0
            FFYCNTSGLF NSIWN..... GSMSN DMGP.....N GTITLQCRIK
A UG U455
            FFYCNTSGLF NGTWNASMQ. .....ES NSTESN.... ETIILPCRIK
AC IN 2130
            FFYCNTSGLF NSTWS..... KR NGTWQSNGTE LNITLPCRIK
AC_RW 92RW
           FFYCDTSGLF NSTWPFNS......T NSTGPN.... GTITLQCRIK
AC SE SE94
ACD_SE_SE8 FFYCNTSGLF NSTWV..... NGSRE SNSTDN.... DTITLPCRIK
           FFYCNTSGLF NSTYN..... PSYN STESVN...E TTIILPCKIK
ACG BE VI1
           FFYCNTTGLF NSTWNDTAT. .....EQKP .....N. DTIRLQCRIK
AD_SE_SE69
           FFYCNTSGLF NSTWN..... NTDSM QBSHSTET.N DTITLPCRIK
AD_SE SE71
           FFYCNTSQLF NSTWNHTST. .....YNST EN..... GTITLPCKIK
ADHK NO 97
           FFYCNTSKLF NSTWQNNGA. .....RLSN S..TE.ST.. GSITLPCRIK
ADK CD MAL
           FFYCNTSALF NFSSETNST. ..... FP.N.... TTLTLPCRIK
AG BE VI11
           AG NG 92NG
           AGHU GA VI
           FFYCNTSGLF NSTWK.... NSTSI NDTVSN... GTITLPCRIK FFYCNTSGLF NKSLLNETS. ....NETT DGAN.... NTÍTLTCRIK
AGU CD Z32
AJ BW BW21
           FFYCNSTQLF NSTWFNSTG. .....NDTE RATNN..T.. ENITLPCRIK
B_AU_VH_AF
           FFYCNTSQLF NSTWNDTG.. ......T WNDTTGNS.. .TITLPCRIK
B CN RL42
           FFYCNSAQLF NSTWNDTK......ES NNTNG......TITLPCRIK
B DE D31 Ü
           FFYCNSTKLF NSTWNNTST. .....WN.. DNGND..... TIILPCRIK
B DE HAN U
           FFYCNSTQLF NSTWFNSTW. .....STEG SNNTEGSD.. .TITLPCRIK
B FR HXB2
B GA OYI_
           FFYCNTSQLF NSTWNDTTR. .....AN.. .STEV..... .TITLPCRIK
B_GB_CAM1 FFYCNTTQLF NTTWLFNGT. ... WNDT EGLNNTER. .NITLPCRIK
B_GB_GB8_C FFYCKTAQLF NSTWNSTGN. ... GTIK SNTTE. .IITLPCRIK
B_GB_MANC_ FFYCNSTQLF NSTWNTGND. .TRES NDTNN..T. GNITLPCRIK
           FFYCNTTQLS NSTWQRSDG, .... TWNR TGGLNETK. ENITLPCRIK
B_KR_WK_AF
B_NL_3202A FFYCNSTQLF NSTWNDTGN. .....VTER SNNNE..... NITLPCRIK
          FFYCNATPLF NSTWNATST. .....LNAT NEENB..... .NITLLCRIK
B_TW_TWCYS
           FFYCKSTQLF NSTWAGNNT. .....WNSS AERSDDTG. GNITLPCRIK
B US BC LO
B US DH123
           PFYCNTKKLF NSTWNGTEG. .....SYNI EGND..... .TITLPCRIK
           FFYCNSTQLF NSTWNDTEK. .....SSG. TEGND..... TIILPCRIK
B US JRCSF
B_US_MNCG_
           FFYCNTSPLF NSTWNGNNT. .....WNNT TGSNN......NITLQCKIK
           FFYCNTAQLF NSTWNVTGG. .....TNG. TEGND..... .IITLQCRIK
B US P896
           FFYCNTTQLF NSTWNSTEG. .....SNNT GGND......TITLPCRIK
B US RF M1
B_US_SF2_K FFYCNTTQLF NNTWRLNHT. ....EG.. TKGND. ... TIILPCRIK
B_US_WEAU1 FFYCNSTQLF NSTWHANGT. ....WKNT EGADN. ... NITLPCRIK
           FFYCNSTQLF NSTWNSTEG. .....NS.. TWSDK..... . IIRLPCRIK
B_US_WR27_
B_US_YU2_M
          FFYCNSTQLF ...WNDTRK. .....LN. .NTGR..... NITLPCRIK
           FFYCNTSGLF NDTVDN.... GTITLPCRIK
BF1 BR 93B
C BR 92BR0
           FFYCNTSSLF NSTYT..... PNST ENITGT..EN SIITIPCRIK
C_BW_96BW0 FFYCNTSRLF NESYS..... FNES HWSND...TN ATITLPCRIK
C_BW_96BWl FFYCNTSKLF NGTYI......QPNS .TEDTP...N STITLPCRIK
C_BW_96BW1 FFYCNTSQLF NSTYN..... S.TY MPS...NNTG TNITLQCRIK
C_BW_96BW1 FFYCNSSKLL NSSYN......GTSY RGTESN...S SIITLPCRIK
C_ET_ETH22 FFYCNTSNLF NSTKL.....E... LFNSS...TN LNITLQCRIK
C_IN_93IN1 FFYCNTSGLF NGTYM..... PTYM PNGTESN.SN STITIPCRIK
C_IN_93IN9 FFYCNTSGLF NGTYN......TSSD GNS.....S STITIPCRIK
C_IN_93IN9 FFYCNTSSLF DSLFN..... PNGT RNDT....N LTITIPCRIK
C_IN_94IN1 FFYCNTSGLF NSTYM..... SGTY MNSSADM.NS SYITIPCRIK
          FFYCNTSGLF NRTYM..... PNDT KSNSSSN.PN ANITIPCRIK
C_IN_95IN2
          FFYCNTTKLF NSTWT..... TNE IMEEFKGTNS STITLPCRIK
CRF01_AE_C
CRF01 AE C
          FFYCNTTALF NSTWI......N.G TMQEVNGTNS GNITLPCRIK
          CRF01 AE C
          FFYCNTTQLF NNTCI......GNE TMK...GCNG .TITLPCKIK
CRF01 AE T
CRF01 AE T
          FFYCNTTQLF NSTWT..... GNE TME...GSNG .TITLPCKIK
CRF01_AE_T FFYCNTTRLF NNTCI......GNK TMK...ECND .TIILPCKIK
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FFYCNTTKLF NNTCL......GNE TMA...GCND .TITLPCKIK
 CRF01_AE_T
           FFYCNTTKLF NSTWR......GNE TIESREGYNK .TIILPCKIK
 CRF01 AE T
           FFYCNTSELF NSTW..... ..NSTWDNSS NHIESNHT.E GNITLQCRIK
 CRF02 AG F
 CRF02_AG_F
           FFYCNTSELF N..... STWDNSL NHTESNHT.E DNITLQCRIK
CRF02_AG_G FFYCNTSGLF NSTWYKN... ..STWYSNST ASSNHTEL.N STITLOCKIK
CRF02 AG N FFYCNTSKLF N.....STWDNSN STANHTGS.N DTITLQCRIK
CRF02_AG_S FFYCNTSNLF NRTWNHNGTW NAPGPFNDTE DKTINGTE.D KTITLQCRIK
CRF02_AG_S FFYCNTABLF NSTWASN... .TNGIWASNI NASNNKDA.N DTITLKCKIK
CRF03_AB_R FFYCNTTKLF NSTWNGTEE. .....LN...NTEG..... DIVTLPCRIK
CRF03_AB_R FFYCNTTKLF NSTWNNTEE. .....SN...NTKG..... DIVTLPCRIK
CRF04_cpx_
          FFYCNTTPLF NSTHMQNGT. .....NIT. S.TDSTN... STITLQCRLK
CRF04_cpx_
          FFYCNTSGLF NSTYMFNST. .....NRTN T.TNGTN... STITLPÇRIK
CRF04_cpx_
           FFYCNTSDLF NRTYMVNKN. .....ETNS T.NTTDE... KIIRLPCRIK
CRF05 DF B
          FFYCDTSKLF NATVFNDTV. .....FNAT MFNND...SD KNIILPCKIK
          FFYCNTSGLF NVTVP.........NNE.......TITLPCRIK
CRF05 DF B
          FFYCNTSNLF NTSDLFNTS. R.G NDTN. TTITLPCKIK
FFYCNTSQLF NNNITDSNE. T TNFTLPCKIK
FFYCNTSQLF NSSIPESNE. T DIITLPCKIK
CRF06_cpx_
CRF06_cpx_
CRF06_cpx_
          FFYCNTSQLF NSSNLNNNS. ..... SDNN..... GTITLPCRIN
CRF06_cpx_
          FFYCNTSGLF NNTWLFNST. .....WNSS QELNGT...E PNITLPCRIK
CRF11_cpx_
CRF11_cpx_
          FFYCNTSGLF NSTWYANDN. .....TSTQ NDMQSN...D .TITLPCRIK
          FFYCNTSGLF NSAWNISGH. .....STGL N.....D.. TIITIPCRIK
D CD 84ZR0
D_CD_ELI K
          FFYCNTSGLF NSTWNISAW. .....NNIT ESNNS.TN.. TNITLQCRIK
D_CD_NDK_M FFYCNTSRLF NSTWNQTNS. . . . . TGFN . . . . . N . . GTVTLPCRIK
          FPYCNTTRLF NSTWKRNNS. .....EWRS D..NT.PD.. ETITLQCRIK
D UG 94UG1
F1_FR_MP41 PFYCDTSGLF NESEKY.... N GTIILPCKIK
F2_CM_MP25 FFYCNTTILF NHTRVNDIL. .....SNNH TR....EN DTITLPCRIK
FFYCNTSGLF NNSILKSNI. ..... SENN. ... DTITLNCKIK
G_BE DRCBL
          FFYCNTSGLF NNNISNIN......N..... ETITLPCKIK
G NG 92NG0
G_SB_SE616 FFYCNTSGLF NSSLLRSNS. ..... SE.N..... GTITLPCKIK
H_BB_VI991 FFYCNTTKLF NSTWTNSSY. ..... TNDT YNSNSTEDIT GNITLQCKIK
H_BE_VI997 FFYCNTSGLF NSSWTGDNI. .....NMPN DTG...... KNITLPCRIK
H_CF_90CF0 FFYCNTSGLF NSSWEMHTN. ...YTSN DTKG...N. ENITLPCRIK
J_SE_SE702 FFYCNTSTLF NSSWDENNI. ...KDTN STNDN. ... TTITIPCKIK
J_SE_SE788 FLYCNTSKLF NSSWDKNSI. .....EATN DTSX..... ATITIPCKIK
K_CD_EQTB1 FSYCDTTDTV DDTEEE.....ED TTITIPCRIK
K_CM_MP535 FFYCNTTKLF NETGE..... N GTITLPCRIK
          FFYCNTSKLF NEELLN.....ETG. ..... EPITLPCRIR
N CM YBF30
          FFYCNTAKMF NYTFS..... CNGTTC SVSNVSQ.G. NNGTLPCKLR
O CM ANT70
O_CM_MVP51 FFYCNTSGMF NYTFIN......CTKSGC QEIKGSNETN KNGTIPCKLR
          FFYCNTSKMF NYTFS..... CIGTNC TSNQNSSNS. NDTRIYCRIK
O SN 99SE
O_SN_99SE
         FFYCNTSQMF NYTFS..... CTRTNC IRQSNSS... INGTISCRIK
U_CD__83C FFYCNTSELF TGIWNG.....TWDK NCTSTESNCT GNITLPCRIK
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501
 00BW0762_1 QIINMWQGVG KAMYAPPIAG NIICKSNITG LLLTRDGGEE N.....TTE
           QIINMWQEVG RAMYAPPIEG NITCKSNITG LLLVRDGGKT ED...NKSE
 00BW0768 2
            QIINLWQEVG RAIYAPPIAG NITCKSNITG LLLTRD.GG. NNS....TTE
 00BW0874 2
           QIINMWQGVG QAMYAPPIAG NITCRSNITG LLLTRDGGIN ...EDDNNTE
 00BW1471 2
00BW1616_2 QIINLWQGVG RAMYAPPIAG NITCKSNITG LLLTRDGGGE N....NSTE
 00BW1686_8 QIINMWQEVG RAIYAPPIAG KITCISNITG TLLTRDGGVS NTTE...GNE
           QIINMWQEVG RAMYAPPIEG NITCNSSITG LLLTRDGGKN S...TNNGTE
 00BW1759 3
           QIINMWQKVG RAMYAPPIAG NITCKSNITG LLLTRDGGNT S....STEE
 00BW1773 2
00BW1783_5 QIINMWQGVG QAIYAPPIAG NITCKSNITG LLLTRDGG.. NN...TENTE
00BW1795_6 QIINMWQKVG RAMYAPPIEG NITCISNITG LLLTRDGG.. YE...ANHTE
00BW1811_3 QIINLWQEVG RAMYAPPIAG NITCKSNITG LLLTRDGGGS NTTN...ATE
00BW1859_5 QIINMWQEVG RAMYAPPIAG NITCKSKITG LLLTRDGGKQ .....NESK
           QIINMWQGVG RAMYAPPIEG NITCNSNITG LLLTRNRGRE NGD...NTTE
00BW1880_2
           QIINMWQGVG RAIYAPPIEG NITCKSNITG LLLTRDGGKG NDT....AE
00BW1921 1
           QIINMWQKVG RGIYAPPIEG SITCNSNITG LLLVRDGG.. IN...TSTVE
00BW2036 1
00BW2063_6 QIINMWQGVG RAMYAPPIAG NITCTSNITG LILTRDGGG. NE...TNETE
00BW2087_2 QIINMWQEVG RAMYAPPIAG NITCKSNITG ILLTRDGGED TKN...KTE
00BW2127_2 QIVNMWQGVG RAIYAPPIAG NITCNSSITG LLLLRDGGTE TENN...RTE
00BW2128_3 QIINLWQEVG RAMYAPPIEG NITCKSNITG LLLTRDGGTN ..N...NNTE
00BW2276_7 QIINMWQGVG RAIYASPIEG SITCKSNITG LLLVHDGG.. NSNT...STE
00BW3819_3 QIINMWQEVG RAIYAPPIAG NITCTSNITG LLLTRDGEPS TE......
00BW3842_8 QVINMWQRVG QAIYAPPIEG IITCNSSITG LLLVRDGD.. NO...TSDTE
           QIINMWQEVG RAIYAPPIRG IITCTSNITG LLLTRDGGNT GGN....TTE
00BW3871_3
00BW3876 9
           QIINMWQEVG RAMYAPPIAG NITCTSNITG LLLTRDGG.N GG....NNTE
00BW3886_8 QFIRMWQRVG QAMYAPPIAG NITCRSNITG LLLTRDG... KNDTE
00BW3891_6 QIINMWQGVG RAMYAPPIAG RIICKSNITG LLLVRDGGQD N...VMNATE
00BW3970_2 QIINMWQKVG RAIYAPPIAG KITCKSNITG LLLVRDGGGG NN....TATE
00BW5031_1 QIINMWQGVG RAMYAPPIAG NIICKSNITG VLLTYDGGEE N.....E
 96BW01B21 QIINMWQGVG RAMYAPPIKG SITCRSNITG LLLTRDGGLN RS...TEEPE
  96BW0407 QIINMWQGVG RAIYAPPIAG NITCVSNITG LLLTWDGGHQ SN.....E
  96BW0502 QIINMWQKVG RAMYAPPIAG NLTCESDITG LLLTRDGGKT G....PNDTE
 96BW06_J4 QIINMWQEVG RAIYAPPIAG NITCKSNITG LLLTRDGGLN NDS.....E
 96BW11_06 QFINLWQEVG RAMYAPPIAG NIICKSNITG LLLTRDG....D...KNDSE
  96BW1210 QIINRWQEVG RAMFAPPIAG NITCKSNITG ILLVRDGGNT SEN....IE
           QIINMWQKVG RAIYAPPIEG NITCSSSITG LLLARDGG.. LD...NVTTE
 96BW15B03
 96BW16_26 QIINMWQGVG RAMYAPPIEG NITCKSNITG LLLVRDGGTE ENN...TGTE
 96BW17A09 QIINMWQGXG QAMYVPPIAC NITCRSNITG LLLTRDGGK. ...VTGNTTE
 96BWMO1_5 QIINMWQGVG RAMYASPIAG NITCKSNITG LLLTRDGG.. NE...TSGIE
 96BWMO3_2 QIINTWQEVG RAIYAPPIAG NIICISNITG LLLTRDGGKT ND...TNDTE
98BWMC12_2 QIINMWQEVG RAMYAPPIAG NITCRSNITG LLLTRD.GGN TTE....TKE
98BWMC13_4 QIINMWQGVG RAMYAPPIAG NITCISNITG LILTRDGG.. VN...RSDTE
98BWMC14_a QIINMWQEVG RAIYAPPIKG NITCESNITG LLLTRDGGSN DTT.....E
98BWMO14_1 QIINMWQGVG QAMYAPPIAG NITCKSNITG ILLTRDGGIN NTN....GTE
98BWMO18_d QIINMWQKVG RAIYAPPIAG NITCSSRITG LLLTRDGGKN .....DTHE
98BWMO36_a QIINMWQEVG RAMYAPPIAG NITCKSNITG LLLVRDGGNN NTT.....E
98BWMO37_d QIINMWQKVG RAMYANPIEG NITCRSNITG LLLENDG... N.......M
99BW3932_1 QIINMWQKVG RAMYAPPIAG NITCKSNITG LLLVRDGGTA TD.....E
99BW4642_4 QIINMWQEVG RAMYAPPIAG NITCQSNITG LLLTRDGGTE TD....NKTE
99BW4745_8 QIINMWQEVG RAMYAPPIEG NITCKSNITG LLLVRDGGGK N...ATNDTE
99BW4754_7 QIINMWQEVG RAMYAPPIAG RIICNSTITG LILTRDGGNT N....NTE
99BWMC16_8 QIINRWQEVG RAMYAPPIAG NITCTSNITG LLLVRDGGRT SD....STKE
A2_CD_97CD QIINMWQRVG RAMYAPPIAG VIKCTSNITG MILTRDG..G KNS....INE
A2_CY_94CY QIINMWQRVG RAMYAPPIAG IIKCTSNITG IILTRDG..G NNG....TNE
A2D 97KR QIVNMWQRVG RAMYAPPING TIKCTSNITG MILTRDGNSG GNA....TNE
A2G_CD_97C QIINMWQRVG RAMYAPPIAG IINCTSNITG IILTRDGEKG GDN....TIE
A BY 97BL0 QIINMWQRVG QAMYAXPIKX SIRCESNITG LLLTRDGXGX TNX...SNE
A_KE_Q23_A QIINMWQRAG QAMYAPPIPG VIKCESNITG LLLTRDGGKD NN....VNE
A_SE_SE659 QIINMWQRAG KAMYAPPIQG VIRCESNITG LILTRDG.GD AG....ENE
A_SE_SE725 QIINMWQRAG QAIYAPPIPG IIRCESNITG LLLTRDG.GV VNS....TNE
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QIINMWQRVG QAMYAPPIRG AIRCKSNITG LLLTRDGGNS NSS....TNE
 A_SE_SE753
             QIINMWQRAG KAIYAPPIPG IIKCVSNITG LILTRDG.GS NNS....TNE
 A_SE_SE853
             QIINMWQRAG QAIYAPPIQG VIRCESNITG LILTRDG.GN DNN...ESE
 A SE SE889
             QIINMWQRTG QATYAPPIPG VIQCRSNITG LLLTRDGGVT NNT...NNE
 A SE UGSE8
 A UG 92UG0
             QIINMWQRVG QAMYAPPIQG VIKCESNITG LILTRDG.GV NSS....DSE
             QIINMWQRVG QAMYAPPIQG VIRCESNITG LLLTRDG.GT NNT....KNE
 A UG U455
             QIINMWQRVG QAMYAPPIQG IIKCVSNITG LILTRDGK.S SNS....TDE
 AC IN 2130
             QIINMWQRTG QAMYAPPIQG VISCVSNITG LLLTRDG.GN NNT....TTE
 AC_RW_92RW
             QIIRMWQRTG QAIYAPPIPG EINCVSNITG LLLTRDG..G NNI....TNE
 AC SE SE94
 ACD_SE_SE8 QIINMWQRVG QAMYALPIRG VIRCESNITG LILTRDG.GN NTS....TNE
 ACG_BE_VI1 QIINMWQEVG RAMYANPIAG NITCNSNITG LLLTRDGGVN ET....TETE
 AD_SE_SE69 QIINMWQRAG RAIYAPPIQG VINCVSDITG LILTRDGGVN .NT.N...E
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 AD_SE SE71
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 ADHK NO 9'7
 ADK CD MAL
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 AG BE VI11
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 AG NG 92NG
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 B DE D31 U
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 B_DE HAN U
            QIINMWQKVG KAMYAPPISG QIRCSSNITG LLLTRDGGNS .N..N..ESE
 B_FR_HXB2
 B GA OYI_
            QIVNMWQEVG KAMYAPPISG QIRCSSKITG LLLTRDGGKN ....TTNGIE
 B GB CAM1
            QIINRWQEVG KAMYAPPITG TISCSSNITG LLLTRDGGRG .E..N..ETE
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            QILNLWQEVG KAMYAPPISG QISCSSNITG LLLTRDGGNT .NT.TGNTTE
B_GB MANC
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B_KR_WK_AF
B_NL_3202A QIINMWQGVG KAMYAPPISG QIRCSSNITG LLLTRDGGKD .E..NKTGTE
B_TW_TWCYS QIINMWQRVG KAMYAPPIEG LIKCSSNITG LMLTRDGGTN .D...SEVE
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B US BC LO
            QIINMWQEVG KAMYAPPISG QIWCSSNITG LLLTRDGGKN .....SSTE
B US DH123
            QIINMWQEVG KAMYAPPIKG QIRCSSNITG LLLTRDGGK. ....NESEIE
B_US_JRCSF
B_US_MNCG_
            QIINMWQEVG KAMYAPPIEG QIRCSSNITG LLLTRDGGKD .T..DTNDTE
            QIINMWQKVG KAMYAPPITG QIRCSSNITG LLLTRDGGNS ....TETETE
B US P896
            QIVNMWQEVG KAMYAPPISG QIKCISNITG LLLTRDGGED .T..T.NTTE .
B US RF M1
B_US_SF2_K QIINMWQEVG KAMYAPPIGG QISCSSNITG LLLTRDGGTN .V..T.NDTE
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B US WEAU1
B_US_WR27_
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BF1 BR 93B
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C_BR_92BR0
C BW 96BW0
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C_BW_96BW1 QIINRWQEVG RAMFAPPIAG NITCKSNITG ILLVRDGGNT SEN....IE
C_BW_96BWl QIINMWQKVG RAIYAPPIEG NITCSSSITG LLLARDGG.. LD...NVTTE
C_ET_ETH22 QIINMWQGVG RAMYAPPIBG IIMCRSNITG LLLTRDGAKE PH....STKE
C_IN_93IN1 QIINMWQEVG RAMYAPPIAG NITCTSNITG LLLVHDGGIK EN.DTENKTE
C_IN_93IN9 QIINMWQEVG RAMYAPPIEG NITCKSNITG LLLVRDGGAE AK...TNNTE
C_IN_93IN9 QIINMWQEVG RAMYAPPIAG NITCKSNITG LLLVRDGGRG ND..TENNTE
C_IN_94IN1 QIINMWQEVG RAMYAPPIAG NITCKSNITG ILLERDG..G SG...SNGTE
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CRF01 AE C
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CRF01 AE C
CRF01 AE C
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CRF01 AE T
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CRF01 AE T
           QIIRMWQGAG QAMYAPPISG IINCVSNITG ILLTRDGGS. ANNTN...NE
CRF01_AE_T QIINMWQGVG QAMYNPPISG NINCVSNITG ILLTRDGGGG NGTNN...BE
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 CRF01_AE_T
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             QIINMWQGAG QAMYAPPING TINCISNITG ILLTRDGGD. NNNTI...NE
 CRF01 AE T
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CRF02 AG F
CRF02 AG F
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CRF02_AG_N QIVNMWQKVG QAMYAPPIQG IIRCDSNITG LLLTRDG.G. NNS....TNE
CRF02_AG_S QIVRMWQKVG QAMYAPPIPG EIRCESNITG LLLTRDG.GN DNN...NTE
CRF02_AG_S QIINMWQKVG QAIYAPPIEG VIRCDSNITG ILLTRDG.GD NTN....GDE
CRF03_AB_R QIINMWQEVG KARYAPPIAG QIRCSSNITG LLLTRDGGNQ .S....NVTE
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D UG 94UG1
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F1_F1_FIN9 QFVNMWQEVG RAMYAAPIAG NITCNSNITG LLLTRDGG.. QS..NNSDSE
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F2_CM_MP25 QIVNMWQRVG QAMYAPPIAG KIQCNSNITG LLLTIDGG.....EGNESE
F2KU_BE_VI QIINRWQGVG QAMYAPPIAG NITCRSNITG MILTRDGGNS N...DTIDNE
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G SE SE616
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O_CM_ANT70 QVVRSWIRGQ SGLYAPPIKG NLTCMSNITG MILQMDNTWN SSNN....NV
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O_SN_99SE_ QVVRSWIQGG SGLYAPPRKG NLTCSSLITG MILQLDMPWN STNNS...NA
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B GA OYI_
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A_BY_97BL0 KNXQDLLALD KAG.LXSXXD ISNWLXYIXI FIIIVGGLIX LRIIFAVLSI
A_KE_Q23_A KNEKELLELD KWANLWSWFD ISNWLWYIKI FIIIVGGLIG LRIVFAVLSV
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A SE SE889
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A SE UGSE8
A UG 92UG0
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C BW 96BW1
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 AG NG 92NG
 AGHU_GA_VI VNRVRQGYSP LSFQTLFP.. NQREP.DRPE GIEEEGGEQG RSRSIRLVNG
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 B AU VH AF
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 B CN RL42
 B_DE D31 U
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 B FR HXB2
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B US WR27
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           LCGAVMQYWL QELKNSATNL LDTIAVSVAN WTDGIILGLQ RIGQGFLHIP
O_SN_99SE_
           LCIAVIQYWL QELQNSATSL LDTIAVAVAN WTVTIILGIQ RIGRGILNIP
O SN 99SE
           ICIAVIQYWL QELQNSATSL LDTLAVAVAN WTDGIILGLQ RIGRGILNIP
U_CD___83C YLGNLVLYWG QELKNSAISL LNATAIVVAE GTDRIIEVGQ RICRAILNIP
```



```
951
                        962
             RRIRQGFEAA LQ
  00BW0762 1
  00BW0768_2
             RRIRQGFEAA LQ
  00BW0874_2
             RRIRQGFEAA LQ
  00BW1471_2
             RRIEQTFEPP LL
  00BW1616_2
             RRIRQGVEAA LQ
             RRIRQGFETA LL
 00BW1686 8
 00BW1759 3
             RRIROGFEAA LQ
 00BW1773_2 RRIRQGFEAA LQ
 00BW1783 5 RRIROGFEAA LQ
 00BW1795_6 TRIRQGFEAA LQ
 00BW1811_3 RRIROGFEAS LL
 00BW1859_5 RRIRQGFEAA LL
 00BW1880_2 TRIRQGFEAA LQ
 00BW1921_1 TRIRQGFEAA LQ
 00BW2036_1 RRIRQGFEAA LQ
 00BW2063_6 RRVRQGFETA LL
 00BW2087 2
            RRIRQGFEVA LL
 00BW2127 2
             TRIRQGFEAA LL
 00BW2128 3 SSIRQGFEAA LQ
 00BW2276 7
            RRIRQGFEAA LL
 00BW3819_3 TRIRQGFEAA LL
 00BW3842_8 RRIRQGFEAA LQ
 00BW3871_3 RRLRQGFEAA LL
 00BW3876_9 RRIRQGFEAA LL
 00BW3886_8 RRIRQGFEAA LL
 00BW3891_6 TRIRQGFEAA LQ
 00BW3970_2 RRIROGFEAS LL
 00BW5031_1 RRIRQGFEAA LQ
96BW01B21 RRIRQGFEAA LQ
   96BW0407 TRIRQGFEAA LQ
   96BW0502 RRIRQGFEAA LQ
  96BW06_J4 RRIRQGFEAA LL
  96BW11_06 RRIRQGFETA LL
  96BW1210 RRIRQGFEAA LQ
  96BW15B03 RRVRQGFEAA LQ
 96BW16_26 RRLRQGFEAA LQ
            TRIRQGLEAA LQ
  96BW17A09
 96BWM01_5
            RRIRQGFEAA LL
 96BWM03_2
            RRIRQGFEAA LL
98BWMC12 2
            .....GFEAA LO
98BWMC13 4
            RRIRQGFETA LL
98BWMC14 a
            RRVRQGFEAA LQ
98BWM014_1
            TRIRQGLEAA LL
98BWM018_d RRIRQGFEAA LQ
98BWM036_a TRIRQGFEAA LL
98BWM037_d RRIRQGFEAA LL
99BW3932_1 RRIRQGFETA LL
            RRIRQGFEAA LQ
99BW4642 4
99BW4745_8
           TRIRQGFEAA LQ
99BW4754_7
           RRIRQGFEAA LQ
99BWMC16_8 RRIRQGFETA LL
A2_CD_97CD RRIRQGLERA LL
A2_CY_94CY RRIRQGLERA LL
A2D___97KR RRIRQGLERA LL
A2G_CD_97C RRIRQGLERA LL
A_BY_97BL0
            RRIRXGAEKA LQ
A_KE_Q23_A VRIRQGLERA LL
A_SE_SE659 RRIRQGFERA LL
A_SE_SE725 RRIRQGFEEA LL
```

```
A_SE_SE753
            RRIRQGFERA LL
A_SE_SE853
             VRIRQGFERA LL
A SE SE889
             RRSKQGLKRA LQ
A_SE_UGSE8
             RRIRQGFER. ..
A_UG_92UG0
            RRIRQGFERA LL
A UG U455
             RRIRQGLERA LL
AC IN 2130
            RRIRQGLERA LL
AC RW 92RW
            SRIRQGFEAA LQ
AC_SE_SE94
            RRIRQGFERA LL
ACD_SE_SE8
            RRIRQGLERA LL
ACG_BE_VI1
            RRIRQGFERA LL
AD_SE_SE69
            ARIRQGLERV LL
AD_SE_SE71
            RRIRQGLERA LL
            RRIRQGFERX LL
ADHK_NO_97
ADK CD MAL
            RRIRQGFERA LL
AG_BE_VI11
            RRIRQGLERA LL
AG NG 92NG
            RRIRQGLERA LL
AGHU GA VI
            RRIRQGLERA LI
AGU_CD_Z32
            RRIRQGLERA LL
AJ BW_BW21
            VRIRQGFERA LL
B_AU_VH_AF
            RRIRQGLERL LL
B_CN_RL42_
            TRIRQGLERA LL
B_DE_D31_U
B_DE_HAN_U
            VRIRQGLERA LL
            RRVRQGLERA LL
B_FR_HXB2_
            RRIRQGLERI LL
B_GA_OYI__
            RRIRQGLERA LL
B GB CAM1
            RRIRQGLERL LL
B GB GB8 C
            TRIRQGLERA LQ
B GB MANC
            VRIRQGLERA LL
B_KR_WK_AF
            RRIRQGLERA LL
B_NL_3202A
            VRIRQGLERA LL
B_TW_TWCYS
            TRIRQGLERA LL
B_US_BC_L0
            RRIRQGLERL LL
B US DH123
            TRIRQGLERA LL
B_US_JRCSF
            TRIRQGLERA LL
B_US_MNCG_
            TRIRQGLERA LL
B_US_P896_
            TRIRQGLERA LL
B US RF M1
            RRIRQGLERA LL
B US SF2 K
            RRIRQGLERL LL
B_US_WEAU1
            B_US_WR27_
            RRIRQGLERV LL
B_US_YU2_M
           VRIRQGLERA LL
BF1 BR 93B
            RRIRQGLERA LL
            RRIRQGFEAA LQ
C_BR_92BR0
C_BW 96BW0
            TRIRQGFEAA LQ
C BW 96BW1
            RRIRQGFETA LL
C_BW_96BW1
            RRIRQGFEAA LO
C_BW_96BW1
            RRVRQGFEAA LO
C ET ETH22
            RRIRQGLEAA LQ
C IN 93IN1
            TRIRQGFEAA LQ
            RRIRQGFEAV LQ
C_IN_93IN9
C_IN_93IN9
            TRIRQGFEIA LQ
C_IN_94IN1
            RRIRQGLEAA LO
C_IN_951N2
            RRIRQGFEAA LO
CRF01_AE_C
            RRIRQGLERA LL
CRF01 AE C
            RRIRQGLERA LL
CRF01 AE C
            RRIRQGLERA LL
CRF01_AE_T
            RRIRQGLERT LL
CRF01 AE T
            RRIRQGLERA LL
CRF01 AE T
            RRIRQGLERA LL
```

```
CRF01 AE T
            RRIRQGLERA LL
CRF01_AE_T
            RRIRQGLERT LL
CRF01_AE_T
            RRIRQGLERA LL
CRF02_AG_F
            RRIRQGLERA LL
CRF02_AG_F
            VRIRQGLERA LL
CRF02_AG_G
            RRIRQGFERA LL
CRF02 AG N RRIRQGFERA LL
CRF02 AG S
            RRIRQGFERA LL
CRF02 AG S
            RRIRQGLERA LQ
CRF03_AB_R RRIRQGAEKA LO
CRF03_AB_R RRIRQGAEKA LQ
CRF04_cpx_ RRIROGLERA LL
CRF04_cpx_
            RRIRQGFEKA LL
CRF04_cpx_
CRF05_DF_B
            RRIRQGLERA LL
            RRIRQGLERA LL
CRF05_DF_B
            RRIRQGLERA LL
CRF06_cpx_
            RRIRQGFERA LL
CRF06_cpx_
            TRIRQGFERA LL
CRF06_cpx_
            RRIRQGAERA LI
CRF06_cpx_
            RRIRQGFERA LL
CRF11_cpx_
            RRIRQGLERA LL
CRF11_cpx_
            RRIRQGFERA LL
D CD 842R0
            TRIRQGLERA LL
D_CD_ELI K
            RRIRQGLERS LL
D CD NDK M
            RRIRQGLERL LL
D_UG_94UG1
            VRIRQGLERA LL
F1 BE VI85
            RRIRQGAERA LL
F1 BR 93BR
           RRIRQGLERA LL
F1_FI_FIN9 RRIRQRVERA LI
F1_FR_MP41 RRIRQGLERS LL
F2_CM_MP25 RRIRQGLERA LL
F2KU_BE_VI
           RRIRQGFERA LL
G_BE_DRCBL
           RRIRQGLERA LL
G_NG_92NG0
G_SE_SE616
            TRIRQGLERA LL
            TRIRQGLERA LL
H_BE_V1991
            RRIROGFERA LL
H_BE_V1997
            RRIRQGLERI LL
H CF 90CF0
            RRIRQGFERS LL
J SE SE702
            RRIRQGLERA LL
J SE SE788
            RRIRQGLERA LL
K_CD_EQTB1
            RRIRQGFERL LL
K_CM_MP535
           RRIRQGLERA LL
N_CM_YBF30
           RRIRQGLERA LI
O CM ANT70
            RRIRQGLERS LL
            RRIRQGAERI LV
O CM MVP51
0 SN 99SE
            RRIRQGLERS LL
O SN 99SE
           RRIRQGLERA LL
U_CD___83C RRIRQGFERA LL
```

Table 13. HIV Nef Sequence Alignment GCC Multiple Sequence File. Written by Omiga 1.1

Name:		Len:	232	Check:	3461	Weight:	1.00
Name:		Len:	232	Check:	5650		
Name:	_	Len:	232	Check:	3483	Weight:	1.00
Name:	_	Len:	232	Check:		Weight:	1.00
Name:		Len:	232	Check:	1504		
Name:	_ _	Len:	232	Check:	1380	Weight:	1.00
Name:	· · · · - ·	Len:	232	Check:	5319	Weight:	1.00
Name:	· · · · · · · · · · · · · · · · · · ·	Len:	232	Check:	156	Weight:	1.00
Name:		Len:	232	Check:	8063	Weight:	1.00
Name:		Len:	232	Check:	3123	Weight:	1.00
Name:		Len:	232	Check:	4460	Weight:	1.00
Name:		Len:	232	Check:	9116	Weight:	1.00
Name:		Len:	232	Check:	4302	Weight:	1.00
Name:		Len:	232	Check:	2737	3	
Name:		Len:	232	Check:	4558	Weight:	1.00
Name:	-	Len:	232	Check:	1020		
Name:	_	Len:	232	Check:	7532	Weight:	1.00
Name:		Len:	232	Check:	3425	Weight:	1.00
Name:		Len:	232	Check:	5136	Weight:	1.00
Name:		Len:	232	Check:	3623	Weight:	1.00
Name:		Len:	232	Check:	993	Weight:	1.00
Name:		Len:	232	Check:	6030		1.00
Name:	· · · · · · · · · · · · · · · · · · ·	Len:	232	Check:	3547	Weight:	1.00
Name:		Len:	232	Check:	1951	Weight:	1.00
Name:	_ ·	Len:	232	Check:	3786	Weight:	1.00
Name:		Len:	232	Check:	3655		1.00
Name:		Len:	232	Check:	8913	Weight:	1.00
Name:		Len:	232	Check:	2223		1.00
Name:		Len:	232	Check:	2176		1.00
Name:		Len:	232	Check:	5261	Weight:	1.00
Name:		Len:	232	Check:	333	Weight:	1.00
Name:	_	Len:	232	Check:	5784	J ·	1.00
Name:	96BW11_06	Len:	232	Check:	4950	Weight:	1.00
Name:	· · · · · · · · · · · · · · · · · · ·	Len:	232	Check:	6118	Weight:	1.00
Name:		Len:	232	Check:	5089	Weight:	1.00
Name:	·	Len:	232	Check:	3957	Weight:	1.00
Name:		Len:	232	Check:	1945	Weight:	1.00
Name:	-	Len:	232	Check:	5827	3	1.00
Name:	96BWM03_2	Len:	232	Check:	2303	Weight:	1.00
Name:	98BWMC12_2	Len:	232	Check:	2423	Weight:	1.00
Name:	98BWMC13_4	Len:	232	Check:	4043	Weight:	1.00
Name:	98BWMC14_a	Len:	232	Check:	3568	Weight:	1.00
Name:	98BWM014_1	Len:	232	Check:	4909	Weight:	1.00
Name:	98BWM018_d	Len:	232	Check:	3505	Weight:	1.00
Name:	_	Len:	232	Check:		Weight:	1.00
Name:		Len:	232	Check:	1912	Weight:	1.00
Name:	_	Len:	232	Check:		Weight:	1.00
Name:	_	Len:	232	Check:.		Weight:	1.00
Name:		Len:	232	Check:	938	Weight:	1.00
Name:		Len:	232	Check:	1379	Weight:	1.00
Name:		Len:	232	Check:	4222	Weight:	1.00
Name:		Len:	232	Check:	2359	Weight:	1.00
Name:		Len:	232	Check:	5163	Weight:	1.00
		Len:	232	Check:	9468	Weight:	1.00
Name:	A2G_CD_97C	Len:	232	Check:	4189	Weight:	1.00
Name:	A_BY_97BL0	Len:	232	Check:	2590	Weight:	1.00

```
Name: A KE Q23
                        Len:
                                232
                                     Check: 2652
                                                  Weight:
                                                             1.00
Name: A_SE_SE659
                                     Check: 9245
                        Len:
                                232
                                                  Weight:
                                                             1.00
Name: A_SE_SE725
                        Len:
                                232
                                     Check: 985
                                                 Weight:
                                                            1.00
Name: A_SE_SE753
                        Len:
                                232
                                     Check: 1638
                                                  Weight:
                                                             1.00
Name: A_SE_SE853
                        Len:
                                232
                                     Check: 2503
                                                  Weight:
                                                             1.00
Name: A SE SE889
                        Len:
                                232
                                     Check: 2327
                                                  Weight:
                                                             1.00
Name: A_SE_UGSE8
                                     Check: 9538
                        Len:
                                232
                                                  Weight:
                                                             1.00
Name: A_UG_92UG0
                        Len:
                                232
                                     Check: 2621
                                                  Weight:
                                                             1.00
Name: A_UG_U455
                        Len;
                                232
                                     Check: 2084
                                                  Weight:
                                                             1.00
Name: AC_IN_2130
                        Len:
                                232
                                     Check: 2406
                                                  Weight:
                                                             1.00
Name: AC RW 92RW
                        Len:
                                232
                                     Check: 3441
                                                  Weight:
                                                             1.00
Name: AC_SB_SE94
                        Len:
                                232
                                     Check: 3488
                                                  Weight:
                                                             1.00
Name: ACD SE SE8
                        Len:
                                232
                                     Check: 3016
                                                  Weight:
                                                             1.00
Name: ACG_BE_VI1
                        Len:
                                232
                                     Check: 5006
                                                  Weight:
                                                             1.00
Name: AD_SE_SE69
                        Len:
                                232
                                     Check: 3362
                                                  Weight:
                                                             1.00
Name: AD SE SE71
                        Len:
                                232
                                     Check: 2262
                                                  Weight:
                                                             1.00
Name: ADHK NO 97
                        Len:
                                232
                                     Check: 8765
                                                  Weight:
                                                             1.00
Name: ADK CD MAL
                        Len:
                                232
                                     Check: 6397
                                                  Weight:
                                                             1.00
Name: AG BE VI11
                                     Check: 6471
                        Len:
                                232
                                                  Weight:
                                                             1.00
Name: AG NG 92NG
                        Len:
                                232
                                     Check: 2880
                                                  Weight:
                                                             1.00
Name: AGHU GA VI
                        Len:
                                232
                                     Check: 9053
                                                  Weight:
                                                             1.00
Name: AGU CD Z32
                                     Check: 523
                        Len:
                                232
                                                 Weight:
                                                            1.00
Name: AJ BW BW21
                        Len:
                                232
                                     Check: 3842
                                                  Weight:
                                                             1.00
Name: B_AU_VH
                        Len:
                                232
                                     Check: 8468
                                                  Weight:
                                                             1.00
Name: B_CN_RL42
                        Len:
                                232
                                     Check: 9366
                                                  Weight:
                                                             1.00
Name: B_DE_D31
                        Len:
                               232
                                     Check: 3989
                                                  Weight:
                                                             1.00
Name: B_DE_HAN
                                     Check: 563
                        Len:
                               232
                                                 Weight:
                                                            1.00
Name: B FR HXB2
                        Len:
                               232
                                     Check: 3184
                                                  Weight:
                                                             1.00
Name: B GA OYI
                                     Check: 5511
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: B_GB_CAM1
                        Len:
                               232
                                     Check: 4779
                                                  Weight:
                                                             1.00
Name: B GB GB8
                        Len:
                               232
                                     Check: 1128
                                                  Weight:
                                                             1.00
Name: B_GB MANC
                        Len:
                                     Check: 2885
                               232
                                                  Weight:
                                                             1.00
Name: B_KR_WK
                        Len:
                               232
                                     Check: 9915
                                                  Weight:
                                                             1.00
Name: B_NL_3202A
                        Len:
                               232
                                     Check: 3135
                                                  Weight:
                                                             1.00
Name: B_TW_TWCYS
                        Len:
                               232
                                    Check: 2211
                                                  Weight:
                                                             1.00
Name: B_US_BC
                        Len:
                               232
                                    Check: 3145
                                                  Weight:
                                                             1.00
Name: B US DH123
                        Len:
                               232
                                    Check: 7019
                                                  Weight:
                                                             1.00
Name: B_US_JRCSF
                                     Check: 4099
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: B_US_MNCG
                        Len:
                               232
                                     Check: 4137
                                                  Weight:
                                                             1.00
Name: B US P896
                                     Check: 4405
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: B US RF
                        Len:
                               232
                                     Check: 450 Weight:
                                                            1.00
Name: B US SF2
                        Len:
                               232
                                    Check: 5413
                                                  Weight:
                                                             1.00
Name: B_US_WEAU1
                        Len:
                               232
                                    Check: 5335
                                                  Weight:
                                                             1.00
Name: B_US_WR27
                        Len:
                               232
                                    Check: 3720
                                                  Weight:
                                                             1.00
Name: B_US_YU2
                        Len:
                               232
                                    Check: 9943
                                                  Weight:
                                                             1.00
Name: BF1_BR_93B .
                        Len:
                               232
                                    Check: 3598
                                                  Weight:
                                                             1.00
Name: C BR 92BR0
                        Len:
                               232
                                    Check: 3908
                                                  Weight:
                                                             1.00
Name: C_BW_96BW0
                                    Check: 3880
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: C_BW_96BW1
                                    Check: 4542
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: C_BW_96BW1
                                     Check: 6118
                        Len:
                               232
                                                  Weight:
                                                             1.00
Name: C_BW_96BW1
                        Len:
                               232
                                    Check: 5089
                                                  Weight:
                                                             1.00
Name: C ET ETH22
                        Len:
                                    Check: 744
                               232
                                                 Weight:
                                                           1.00
Name: C IN 93IN1
                        Len:
                                    Check: 943
                               232
                                                 Weight:
                                                            1.00
Name: C IN 93IN9
                                    Check: 1241
                        Len:
                               232
                                                 Weight:
                                                             1.00
Name: C_IN_93IN9
                        Len:
                               232
                                    Check: 9885
                                                  Weight:
                                                             1.00
Name: C_IN_94IN1
                        Len:
                               232
                                    Check: 6448
                                                  Weight:
                                                             1.00
Name: C_IN_95IN2
                        Len:
                               232
                                    Check: 5597
                                                  Weight:
                                                             1.00
Name: CRF01_AE_C
                        Len:
                               232
                                    Check: 1052
                                                  Weight:
                                                            1.00
Name: CRF01_AE_C
                        Len:
                               232
                                    Check: 744
                                                 Weight:
                                                            1.00
Name: CRF01_AE_C
                        Len:
                               232
                                    Check: 1265 Weight:
                                                             1.00
```

```
Name: CRF01 AE T
                        Len:
                               232
                                    Check: 697 Weight:
                                                          1.00
 Name: CRF01_AE_T
                        Len:
                               232
                                    Check: 8468
                                                Weight:
                                                           1.00
 Name: CRF01_AE_T
                        Len:
                               232
                                    Check: 9246
                                                 Weight:
                                                           1.00
 Name: CRF01_AE_T
                        Len:
                               232
                                    Check: 8105
                                                 Weight:
                                                           1.00
 Name: CRF01_AE_T
                        Len:
                               232
                                    Check: 9948
                                                 Weight:
                                                           1.00
 Name: CRF01 AE T
                                    Check: 9460
                        Len:
                               232
                                                 Weight:
                                                           1.00
 Name: CRF02 AG F
                                    Check: 925 Weight:
                        Len:
                               232
                                                          1.00
 Name: CRF02 AG F
                        Len:
                               232
                                    Check: 9559
                                                Weight:
                                                           1.00
 Name: CRF02 AG G
                        Len:
                                    Check: 399
                               232
                                                Weight:
                                                          1.00
 Name: CRF02 AG N
                        Len:
                                    Check: 2782 Weight:
                               232
                                                           1.00
 Name: CRF02_AG_S
                        Len:
                               232
                                    Check: 538 Weight:
                                                          1.00
 Name: CRF02 AG S
                                    Check: 6700 Weight:
                        Len:
                               232
                                                           1.00
 Name: CRF03_AB_R
                        Len:
                               232
                                    Check: 6784
                                                Weight: .
                                                           1.00
 Name: CRF03_AB_R
                        Len:
                               232
                                    Check: 3106 Weight:
                                                           1.00
 Name: CRF04_cpx_
                        Len:
                               232
                                    Check: 1551 Weight:
                                                           1.00
 Name: CRF04_cpx_
                                    Check: 5866 Weight:
                        Len:
                               232
                                                           1.00
 Name: CRF04 cpx
                        Len:
                               232
                                    Check: 7925
                                                 Weight:
                                                           1.00
 Name: CRF05 DF B
                        Len:
                               232
                                    Check: 3625
                                                 Weight:
                                                           1.00
 Name: CRF05 DF B
                        Len:
                               232
                                    Check: 5585
                                                 Weight:
                                                           1.00
 Name: CRF06_cpx_
                        Len:
                               232
                                    Check: 3770
                                                 Weight:
                                                           1.00
 Name: CRF06_cpx_
                                    Check: 4202
                        Len:
                               232
                                                 Weight:
                                                           1.00
 Name: CRF06_cpx_
                        Len:
                               232
                                    Check: 5376
                                                 Weight:
                                                           1.00
 Name: CRF06_cpx_
                        Len:
                               232
                                    Check: 1869
                                                 Weight:
                                                           1.00
 Name: CRF11_cpx_
                        Len:
                               232
                                   Check: 3479
                                                 Weight:
                                                           1.00
 Name: CRF11_cpx_
Name: D_CD_84ZR0
                        Len:
                               232
                                    Check: 3712
                                                 Weight:
                                                           1.00
                        Len:
                               232
                                    Check: 1380
                                                 Weight:
                                                           1.00
 Name: D_CD_ELI
                        Len:
                               232
                                    Check: 4418
                                                 Weight:
                                                           1.00
 Name: D CD NDK
                                    Check: 4588
                        Len:
                               232
                                                 Weight:
                                                           1.00
 Name: D UG 94UG1
                        Len:
                               232
                                    Check: 2178
                                                 Weight:
                                                           1.00
 Name: F1 BE VI85
                        Len:
                               232
                                    Check: 4350
                                                 Weight:
                                                           1.00
 Name: F1_BR_93BR
                        Len:
                                    Check: 7703
                               232
                                                 Weight:
                                                           1.00
 Name: Fl_FI_FIN9
                        Len:
                               232
                                    Check: 5036
                                                 Weight:
                                                           1.00
 Name: F1_FR_MP41
                        Len:
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                                    Check: 84 Weight:
                                                         1.00
 Name: F2_CM_MP25
                        Len:
                               232
                                    Check: 2622 Weight:
                                                           1.00
 Name: F2KU BE VI
                        Len:
                               232
                                    Check: 2193
                                                 Weight:
                                                           1.00
 Name: G BE DRCBL
                        Len:
                               232
                                    Check: 2548 Weight:
                                                           1.00
 Name: G_NG 92NG0
                                    Check: 3608
                        Len:
                               232
                                                Weight:
                                                           1.00
 Name: G_SE_SE616
                        Len:
                               232
                                    Check: 2716
                                                Weight:
                                                           1.00
 Name: H BE VI991
                        Len:
                               232
                                    Check: 1561
                                                Weight:
                                                           1.00
 Name: H BE VI997
                        Len:
                              232
                                    Check: 663 Weight:
                                                          1.00
 Name: H CF 90CF0
                       Len:
                              232
                                    Check: 1804
                                                Weight:
                                                           1.00
 Name: J_SE_SE702
                       Len:
                              232
                                    Check: 1615
                                                Weight:
                                                           1.00
Name: J_SE_SE788
                       Len:
                                                Weight:
                               232
                                    Check: 1704
                                                           1.00
 Name: K_CD_EQTB1
                       Len:
                              232
                                    Check: 4783
                                                 Weight:
                                                           1.00
 Name: K_CM_MPS35
                       Len:
                              232
                                    Check: 2033
                                                 Weight:
                                                           1.00
Name: N CM YBF30
                       Len:
                              232
                                    Check: 6419
                                                Weight:
                                                           1.00
Name: O CM ANT70
                                    Check: 8742
                       Len:
                               232
                                                Weight:
                                                           1.00
Name: O_CM_MVP51
                       Len:
                              232
                                    Check: 5835
                                                Weight:
                                                           1.00
Name: O_SN_MP129
                                    Check: 8625
                       Len:
                              232
                                                 Weight:
                                                           1.00
Name: O_SN_MP130
                       Len:
                              232
                                    Check: 8793
                                                 Weight:
                                                           1.00
Name: U_CD 83C
                       Len: 232
                                    Check: 1586
                                                           1.00
                                                Weight:
00BW0762_1
           MGGKWSKSS. IVGWPAVRER IR....RTDP ...........AAEGVG
00BW0768_2
           MGGKWSKSSI V.GWPEVRER IRR..TEP.. ......AAEGVG
00BW0874_2
           MGGKWSKSS. LTGWPAVRER IR....RTEP ...........AAEGVG
00BW1471 2
           MGGKWSKSS. IVGWPAVKER IRR..TNPR. ...... .TERAAVGVG
00BW1616 2
           MGGKWSKRS. KADWPAVREK LR....TTEP ............AAEGVG
00BW1686 8
00BW1759_3
           MGNKWSKS.....WPAVRER IRR..TRPAR ...... GNEPAAEGVG
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00BW1773_2	MGSKWSKSS	C V.GWPKVRE1	IRRTEP		AAEGVG
00BW1783_5	MGNKWSKS	· · · · WPAIRER	R. IRR. TNPAA		ERTRANEGUC
00BW1795 <u>6</u>	MGGKWSKSS.	VVGWPAIRER	MRR		TEDANECUC
00BW1811_3	MGGKWSKSC.	. KIGWPAVRER	MRR		TEDAUECUC
00BW1859_5	MGGKWSKSG.	KVGWPEVRER	MRRTRPAA	EGG	DSAAFGVG
00BW1880_2	MGGKWSKSS.	LVGWPAVRER	IRTTAP		
00BW192T_1	MGGKWSKSS.	IVGWPAVRER	MRKTEP		AAROVO
00BW2036_1	MGGKWSKSS.	IVGWPAVRER	IRR	• • • • • • • • • •	.TEPAAEGVG
00BW2063_6	MGGKWSKSSI	I.GWPAVRER	MRK AED	• • • • • • • • • • •	AAEGVG
00BW2087 2	MGSKWSKSS.	IVGWPAVRER	TRR T		AAEGVG
00BW2127 2	MGGKWSKSSI	I.GWPAIRER	TRP TED	• • • • • • • • • • • • • • • • • • • •	RTEPAAEGVG
00BW2128 3	MGSKWSKCSI	T.GWPAVPER	TDD ACD	• • • • • • • • • • • • • • • • • • • •	· · · · AAEGVG
00BW2276 7	MGSKWSKC		MDD AMDAR	EAGRAAP	AAVGVG
00BW3819 3		. N GMBDAKEK	MRR. ATPAA	EAGRAAP	AAEGAAPGVG
00BW3842 8	MGGKWSKGR.	V.GWPDVRER	MRKARPAV	RERRROTEPA	AEGVAAEGVG
00BW3871 3	MGSKWSKRS.		MRR		. TEPAAEGVG
00BW3876 9	MGGKWSKSS.	IVEWPAVRER	LRKTEP		AAEGVG
00BW3886 8		IVGWPAVRER	IRQTGAR.		AAEGVG
00BW3891 6	MGGKWSKSS.	IVGWSAVRER	MKRTEP		AAEGVG
	MGGKWSKSS.	IVGWPTVRER	MRRTQP		AAEGVG
00BW3970_2	MGSKWSKRS.	TAGWPAVRER	MRR. TOPAA	EG	TOCARDONO
00BW5031_1	MGGKWSKSS.	LVGWPEVRDR	IRRTDP		AAFGUG
96BW01B21	MGGVM2X22T	V.GWPAVRER	IRR. TEP		3 7 7 7 7 7 7
96BW0407	MGGKWSKSSI	V.GWPAVRER	MRRAEP		AAEGUG.
96BW0502	MGGKWSK	CSGWPAVRER	MRR. TRPAV	FCD	THE CAN HOUSE
96BW06_J4	MGGKWSKSS.	IVGWPAVRER	IRRTDP		DARCIM
96BW11_06	MGGVM2V22T	I.GWPAIRER	IRRTEPAA	ER. V	GAAAECUC
96BW1210	MGNKWSKG	WPAVRDR	IRR. TEPAT		EDVVECTO
96BW15B03	MGGKWSKSS.	IVGWPAVRER	IRR	• • • • • • • • • • • • • • • • • • • •	TEDAREGVG
96BW16_26	MGGKWSK	WPAVRER	MRR TR	• • • • • • • • • •	· IEPAAEGVG
96BW17A09	MGXKWSKRS.	IVGWPNVRER	TPP THIDIT	ER	VG
96BWM01 5	MGSKWSKSSI	I.GWPAVRER	TRK TEDDY	ER	EAERAAVGVG
96BWM03 2	MGGKWSKSS.	TVGWDAVDED	MDD TDDGA	30	. TEPAAEGVG
98BWMC12 2	MGSKWSKSS.		MR. IRPGA	AE	····GVG
98BWMC13 4	MGGKWSKSS.	IIGWDAUDED	MRRTEP	• • • • • • • • •	AAEGVG
98BWMC14 a	MGGKWSKSS.	LUCWDDVDDD	MRK	••••••	. TEPAAEGVG
98BWMO14 1	MGSKLSKSK.	LUGWPDVRER	IRKPRP	KP	AAEGVG
98BWM018 d	MGGKWSKSS.	IVGWPAIRER	LR		RTEPAAEGVG
98BWMO36_a		IVGWPAVRER	IRQTDPRE	RIR	QTEPAAEGVG
_	MCGKWSKSSI	V.GWPAVRER	IRRTEPRR	• • • • • • • • • • • • • • • • • • • •	. AEPAAECVG
98BWMO37_d	MGGKWSKSS.	IVGWPEVRER	LRRTAP	• • • • • • • • • • •	AAEGVG
99BW3932_1	MGGKWSKRKI	V.QWPTVRER	LRRTEP		AEGVG
99BW4642_4	MGGKWSKSS.	IVGWPAVRER	IRRTOPAA	EG	T/C
99BW4745_8	MGSKLSKSC.	TAGWPTVRER	IROAEP		AARCUC
99BW4754_7	MGGKWSKSS.	IVGWANVRER	MRR		. TEDA AUGUA
99BWMC16_8	MGNKWSKS	WPAVRER	IRR. TEPAV	RV D	PTPDAABOUG
A2_CD_97CD	MGGKWSKRT.	IVGWPEIRER	MRRTPPAA	EGVP	DTDDAARCUC
A2_CY_94CY	MGGKWSKKS.	IPGWPAIRER	MRRTPPTAOR	TE	AVEDAADOVO
A2D97KR	MGGKWSKRS.	LPGWPAIRER	MRRTPPAAER	TD	DAN NAPOVO
A2G_CD_97C	MGSKWSKSS.	IVGWPAVRAR	TR OTPR		PAR. AAEGVG
A_BY_97BL0	XXGKWSKSS.	IXXWPOVXER	TRRADAD	• • • • • • • • • • • • • • • • • • • •	AAEGVG
A KE Q23	MGGKWSKSS.		MDDADD	• • • • • • • • • • • • • • • • • • • •	AARXVG
A_SE_SE659	MGGKWSKSS.	TVGWDETDED	MDDADO	• • • • • • • • • • • • • • • • • • • •	AAPGVG
A_SE_SE725	MGSKWSKSS.	TUCMDEVDED	I DOWN A A A DO	• • • • • • • • • •	AAAPGVG
A SE SE753		TUCHDEUDED	ĻĶŲI LAAAKG	••••••	VG
A_SE_SE853	MCCKWCYDC	IVGWPEVRER	TKKAPP	• • • • • • • • • • •	AATGVG
A SE SE889	MCCKMeree	KEGWSEVREK	TKÜL	• • • • • • • • • •	PPAAKGVG
A_SB_UGSE8	MCMMMON	IVGWPKVRER	MART'PP	• • • • • • • • • •	AAKGVG
A_UG_92UG0	MCMIRACECC	GWPEVRER	IRQARAPAHT	• • • • • • • • • •	PAPTAATGVG
A_UG_92UGU A_UG_U455	MGNKWSKSC.	IVGWPEVRER	IROTPTAARE	RTR	OAPTAAKGVO
	MGGKWSKKS.	RVEWPEVRKR	MRETPA		AAKCUC
AC_IN_2130 AC_RW_92RW	MGGKWPKSS.	VVGWPEVRER V.GWPAVRER	IRRTPA		AADOUG

AC SE SE94	MGGKWSKSS.	TTGWPOTPED	TRRMAN		
ACD SE SE8		V. GWPAVRER	TRR mpn		AATGVG
ACG_BE_VI1	MGGKWSKRS.	KARMBOARE	MRC MRT.		· · · · AAEGVG
AD SE SE69	MGGKWSKSS.	TUCWDAUDED	MRQTPIAA	EAEG	AAAEGVG
AD_SE_SE71	MGGKWSKSS.	IVCWDEVDED	IRRT.,		DPAAEGVG
ADHK_NO_97	MGGKWSKSS.	IVCHDATED	MRRARAP		SAAPGVG
ADK CD MAL		IVGWPAIRER	MRRAEP		· · · · AAEGVG
AG BE VI11	MGGKWSKSS.	IVGWPKIRER	IRRTPPTETG		VGAVSQD
	MGGRWSKSS.	PVGWSRVRER	MRRTPPAA	EG	AAAEGVG
AG_NG_92NG	IGGKWSKSS.	IVGWPAVRER	IRQTP		PAEGVG
AGHU_GA_VI	MGGEWSRSS.	IVGWSTIRER	MRRAEP		777000
AGU_CD_Z32	MGNKWSKG	WPAVRER	IRQTPPAP	P	AAEGVG
AJ_BW_BW21	MGSNWSKS.S	LIGWPQVRER	MKRAP	A P	AAFGVG
B_AU_VH	MGGKGSKRI.	RSEWPTVRER	IIQAEPAA	AG	VC
B_CN_RL42	MGGKWSKHS.	MFGWPSVRER	MKRAEPAA	DG	VC
B_DE_D31	MGGKWSKSS.	VVGWPAIRER	MK		DAFDAAFOUG
B_DE_HAN	MGGKWSK	CSGWPTVRER	MKOAEP		EDY YDGAG
B_FR_HXB2	MGGKWSKSS.	VIGWPTVRER	MR		DAEDAADDUG
B_GA_OYI	MGGKWSKCS.	MKGWPTIRER	MKR AELOP	DF	DARFOUG
B_GB_CAM1	MGGKWSKRS.	LGGWSAVRER	MOR AED	FB	DATERALGYG
B_GB_GB8	MGGKLSKRS.	MFGWSRVRDR	MOO APP	• • • • • • • • • •	RAEPAAEGVG
B GB MANC	MGGKWSKSR.	KIGWPTVRER	MKO ADDYE	ECD veve	AAEGVG
B KR WK	MGGKWSKRS	VPGWNTIRKR	MRD AFRA	EGRKK	QAEPAAEGVG
B NL 3202A	MGGKWSKSS	WIGNDITER	MKKAEPAA	EG	VG
B TW TWCYS	MGGKWSKDS	VVGWPAIRER	TRO TRO	• • • • • • • • •	RAEPAADGVG
B US BC	MCCKWCKDM	IPGWSNIRER	IRQAEPA.	• • • • • • • • • • • • • • • • • • • •	AADGVG
B US DH123	MCCKI SKCC	EGGWHAVRER	MR	• • • • • • • • • • •	RAEPAADGVG
B US JRCSF	MCCMICKTO	GVGWSTVRER	MRRAEPAA	DR	EP.AVGVG
B_US_MNCG	MCCIVICIO	VPGWSTVRER	MRRAEPAT	DRVR	QTEPAAVGVG
	MGGKWSKR	VTGWPTVRER	MRRAEP		. AELAADGVG
B_US_P896	MGGKWSKRR.	AEGWQTIRER	MRRAEPA		EPAADGVG
B US RF	MGGKWSKSK.	MGGWPAVRER	MOK VEDVV	DC	
5 5 5 5 5			MQICAEPAA	DG	VG
B_US_SF2	. Chicampon	MGGWSAIRER	MRR. AEP.		RAEPAADGVG
B_US_WEAU1	MGGIWSKRS.	GSGWPAIRER	MKR AEDAA	rc	RAEPAADGVG
B_US_WEAU1 B_US_WR27	MGGIWSKRS. MGGKWSKRS.	GSGWPAIRER VGGWPAIRER	MKRAEPAA MX	EG	RAEPAADGVGVG
B_US_WEAU1 B_US_WR27 B_US_YU2	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS.	GSGWPAIRER VGGWPAIRER MAGWPTVRER	MKRAEPAA MX MRRAEPAA	EG	RAEPAADGVGVG RAEPAAEGVG
B_US_WEAU1 B_US_WR27	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS.	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER	MKRAEPAA MX MRRAEPAA LROTP	EGMR	RAEPAADGVG RAEPAAEGVG RAEPAADGVG
B_US_WEAU1 B_US_WR27 B_US_YU2	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER V.GRPAIRER	MRRAEP MKRAEPAA MX MRRAEPAA LRQTP MRRAP	EGMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP MRR.AP	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP MRR.AP	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP MRR.AP MRR.TEP MRR.TEPAA	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK MGNKWSKG	GGWSAIRER GSGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDRWPAVRDR	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP MRR.AP MRR.TEP MRR.TEPAA IRR.TEPAT	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGGAAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK MGNKWSKG. MGGKWSKSS.	GSGWPAIRER VGGWPAIRER MAGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER	MRR.AEP. MKR.AEPAA MX.AEPAA MRR.AEPAA LRQ.TP. MRR.AP. MRR.TEP. MRR.TEPAA IRR.TEPAT IRR	EGMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGGAAAEGVGEPAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK MGNKWSKG MGGKWSKSS.	GSGWPAIRER VGGWPAIRER WAGWPTVRER IVGWPAIRER V.GRPAIRER I.EWPTIRDR I.EWPTIRDR IVGWPAVRER V.GWPAVRER V.GWPAVRER V.GWPAIRER	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP. MRR.AP. MRR.TEP. MRR.TEPAA IRR.TEPAT IRR.AAP	EGMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGGAAAEGVGEPAAEGVG .TEPAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK MGNKWSKG MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI	GSGWPAIRER VGGWPAIRER WAGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDRWPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER	MRR.AEP. MKR.AEPAA MX MRR.AEPAA LRQ.TP. MRR.AP. MRR.TEP. MRR.TEPAA IRR.TEPAT IRR.AP. MRR.AEP.	EGMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGGAAAEGVGEPAAEGVG .TEPAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKRSK MGNKWSKG. MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI	GSGWPAIRER VGGWPAIRER WGWPTVRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDRWPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER	MRR.AEP. MKR.AEPAA MX.AEPAA MRR.AEPAA LRQ.TP. MRR.AP. MRR.TEP. MRR.TEPAA IRR.TEPAT IRR.AAP. MRR.AEP. MRR.AEP.	EGMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGGAAAEGVGEPAAEGVG .TEPAAEGVG .TEPAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKSSI MGGKWSKSSI MGGKWSKSS. MGGKWSKSS. MGGKWSKSS. MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI	GSGWPAIRER VGGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAVRER	MRR.AEP. MKR.AEPAA MX.AEPAA MRR.AEPAA LRQ.TP.MRR.TEP. MRR.TEPAA IRR.TEPAT IRR.AEP. MRR.AEP. MRR.AEP. MRR.AEP. MRR.TEP	ERMR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGEPAAEGVGEPAAEGVGTEPAAEGVGAAEGVGAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9 C_IN_94IN1	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGSKWSKSS. MGGKWSKSSI MGGKWSKSSI MGGKWSKSSI MGGKWSKSSI MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI	GSGWPAIRER VGGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER	MRR.AEP. MKR.AEPAA MX.AEPAA MRR.AEPAA LRQ.TP.MRR.TEP. MRR.TEPAA IRR.TEPAT IRR.AEP. MRR.AEP. MRR.AEP. MRR.TOP.	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGEPAAEGVG .TEPAAEGVG .TEPAAEGVGAAEGVGAAEGVGAAEGVGAAEGVG
B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9 C_IN_94IN1 C_IN_95IN2	MGGIWSKRS. MGGKWSKRS. MGGKWSKRS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKSSI MGGKWSKSSI MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI	GSGWPAIRER VGGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER	MRR. AEP. MKR. AEPAA MX MRR. AEPAA LRQ. TP MRR. TEP MRR. TEPAA IRR. TEPAT IRR. AAP MRR. AEP MRR. TQP MRR. TQP MRR. TQP MRR. TQP	ER MR	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGAAEGVGAAEGVGEPAAEGVGEPAAEGVGTEPAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVG
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B_US_WEAU1 B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9 C_IN_94IN1 C_IN_95IN2 CRF01_AE_C CRF01_AE_C CRF01_AE_C CRF01_AE_T	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKSSI MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKSI	GSGWPAIRER VGGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPOVRER IVGWPQVRER IVGWPVRER IVGWPKVRER	MRR. AEP. MKR. AEPAA MX	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAAEGVGPAAEGVGPAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAEGVGAEGVGAEGVGBEGVG
B_US_WEAU1 B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9 C_IN_94IN1 C_IN_95IN2 CRF01_AE_C CRF01_AE_C CRF01_AE_T CRF02_AG_F CRF02_AG_F CRF02_AG_F	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGSKWSKSS. MGNKWSKCST MGGKWSKSKS. MGNKWSKG MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKS.	GSGWPAIRER VGGWPAIRER VGGWPAIRER VGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPOVRER IVGWPQVRER IVGWPQVRER IVGWPQVREK IVGWPQVREK IVGWPQVREK IVGWPQVREK IVGWPQVRER IVGWPVRER IVGWPVRER IVGWPVRER IVGWPVRER IVGWPVRER IVGWPVRER	MRR. AEP. MKR. AEPAA MX	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAADGVGPAAEGVGPAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAEGVGAEGVGBEGVG
B_US_WEAU1 B_US_WEAU1 B_US_WR27 B_US_YU2 BF1_BR_93B C_BR_92BR0 C_BW_96BW0 C_BW_96BW1 C_BW_96BW1 C_ET_ETH22 C_IN_93IN1 C_IN_93IN9 C_IN_93IN9 C_IN_93IN9 C_IN_94IN1 C_IN_95IN2 CRF01_AE_C CRF01_AE_C CRF01_AE_T	MGGIWSKRS. MGGIWSKRS. MGGKWSKRS. MGGKWSKSS. MGSKWSKSS. MGNKWSKCST MGGKWSKSSI MGGKWSKSS. MGGTMSKCSP MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKCSI MGGKWSKS.	GSGWPAIRER VGGWPAIRER VGGWPAIRER IVGWPAIRER V.GRPAIRER V.GWPAVRER I.EWPTIRDR I.WPAVRDR IVGWPAVRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPAIRER V.GWPOVRER IVGWPQVRER IVGWPVRER IVGWPKVRER	MRR. AEP. MKR. AEPAA MX MRR. AEPAA LRQ. TP MRR. TEP MRR. TEPAA IRR. TEPAT IRR. AAP MRR. AEP MRR. TQP MRR. TQP MRR. TEP MRR. TEP MRR. TEP MRR. TEP MRR. TEP MRR. TEP IRR. TPAAA IRQ. TPVAE IRQ. TPVAE IRQ. TPVAE IRQ. TPPAA I	EG	RAEPAADGVGVG RAEPAAEGVG RAEPAAEGVGPAAEGVGPAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAAEGVGAEGVGAEGVGAEGVGAEGVG

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A SE SE753
           EREVLKWKFD SRLALKHRAQ E.LHPEFYKD C.
A_SE_SE853 ERETLMWKFD SKLALKHRAH E.LHPEYFKN C.
A_SE SE889
           ERETLMWKFD SRLALTHRAR E.LHPEFYKD C.
A_SE_UGSE8 ERETLMWKFD PHLAFKHRAF E.LHPEYYKN ..
A_UG_92UG0
            EKETLRWKFD SSLARVHKAR E.LHPEFYKD C.
            EKEVLMWKFD STLALKHRAY E.LHPEFYKD ..
A UG U455
AC IN 2130
            YGEVLQWKFD SHLAYKHQAR E.RHPEFYKD C.
AC_RW_92RW
           DREVLKWKPD SHLAHRHMAR E.LHPEYYKD C.
AC SE SE94
           ERETLYWRFD SRLALKHLAR E.KHPEFYKD C.
ACD SE SE8
           DKEVLRWKFD SQLARRHMAR E.MHPEYYKD C.
            DREVLVWRFD SRLALKHIAK E.KHPEYFKD C.
ACG BE VI1
           EREVLMWRFN SRLAFEHKAH Q.LHPEYYKD C.
AD_SE_SE69
AD_SE_SE71
           EKEVLKWQFD SRLALKHLAR E.KHPEFYKD C.
ADHK NO 97
            EXEVLMWRFD SRLAFKHRAR E.LHPEFYKD C.
ADK CD MAL
            EREVLKWKFD SSLALRHRAR E.QHPEYYKD C.
            EREVLVWKFD SMLAFKHRAR E.LHPEYYKD C.
AG_BE_VI11
AG NG 92NG
           DREVLVWRFD SSLARRHIAR E.QHPEYYKD C.
AGHU GA VI
           EREVLMWKFD SSLAREHVAR K.LYPEFFKD C.
AGU CD Z32
           EREVLMWKFD SSLARKHLAR E.MHPEFYKD ..
AJ BW BW21
           DREVLMWKFD SSLARRHLAR E.KHPEFYKD C.
  B AU VH EKEVLMWKFD SRLAVHHMAR E.LHPEYYKN ..
 B CN RL42 EREVLMWKFD SRLAIHHMAR E.MHPEYHKD C.
  B_DE_D31 EREVLVWRFD SRLAFKHMAR E.LHPEYYKN ..
  B_DE_HAN EREVLKWKFD SHLAFHHKAR E.LHPEYYKD C.
 B FR HXB2
           EREVLEWRFD SRLAFHHVAR E.LHPEYFKN C.
           EKEVLVWKFD SRLAFRHMAR E.VHPEYYKD C.
  B GA OYI
           EKEVLMWKFD SRLAFHHMAR E.KHPEFYKD C.
 B GB CAM1
  B GB GB8
           EKEVLVWKFN SRLAFHHMAR E.LHPEFYKD C.
 B GB MANC
           EKEVLVWKFD SRLAFHHVPD E.LHPEYYKD C.
   B_KR_WK
           EGEVLVWRFD SRLAFHHMAR E.KHPEYYKD C.
           EREVLEWRFD SRLAFHHMAR E.LHPEYYKD C.
B NL 3202A
           EKEVLVWRFD STLAFHHRAR E.LHPEYYKX C.
B TW TWCYS
           EREVLEWRFD SRLAFHHMAR E.LHPEYYKN R.
  B US BC
B_US_DH123
           EKEVLLWKFD SRLAYHHMAR B.LHPEYYKN C.
B_US_JRCSF
           EKEVLVWKFD SKLALHHVAR E.LHPEYYKD C.
           EREVLVWKSD SHLAFQHYAR E.LHPEYYKN C.
 B US MNCG
           ERQVLVWRFD SRLAFHHVAR E.LHPEYFKN ..
 B US P896
  B US RF
           EKEVLVWKFD SRLAFHHVAR E.KHPEYYKD C.
  B US SF2
           EKEVLVWRFD SKLAFHHMAR E.LHPEYYKD C.
B US WEAU1
           EKEVLMWKFD SKLAFHHVAR E.LHPEYFKD C.
 B US WR27
           EKEVLVWKFD SRLAFHHKAR E.LHPEYYKN ..
  B US YU2
           EREGLEWRFD SRLAFHHVAR E.LHPEYYKN ..
           DRETLQWRFD SRLAFHHMAR E.LHPEYYKD C.
BF1 BR 93B
           HREVLOWKFD SLLARRHMAR E.LHPEYYKD C.
C BR 92BR0
C_BW_96BW0
           DGEVLRWKFD SHLAHRHMAR E.LHPEYYKD C.
C_BW_96BW1
           HKEVLKWKFD SQLARRHLAR E.LHPEFYKD C.
C_BW_96BW1
           DREVLKWKFD SSLARRHLTR E.KHPEYYKD C.
C BW 96BW1
           DKEVLMWKFD SHLARRHMAR E.LHPEYYKD C.
           DREVLKWKFD SHLARRHMAR E.LHPEYYKD C.
C ET ETH22
C IN 93IN1
           HREVLKWKFD SQLARRHMAR E.LHPEFYKD C.
C IN 93IN9
           HREVLOWKFD SLLAHRHRAR E.LHPEFYKD C.
C_IN_93IN9
           HREVLOWKFD SHLAHRHMAR E.LHPEYYKD C.
```

```
C IN 94IN1 HREVLMWK.. .QLAHRHIAR E.LHPEFYKD C.
C IN 95IN2 HNEVLVWKFD SQLAHKHRAR E.LHPEFYNK DC
CRF01_AE_C
          EREVLMWKFD SSLARRHIAR E.LRPEYYKD C.
CRF01_AE_C
           EREVLMWKFD SSLARRHIAR E.LHPEYYKD ..
           EREVLMWKFD SSLARRHIAR E.LHPEYYKD C.
CRF01_AE_C
CRF01 AE T
           EREVLMWKFD SALARKHTAR E.LHPEYYKD C.
CRF01_AE_T EREVLMWKFD STLARKHIAR B.QHPEFYKD C.
CRF01 AE T EREVLIWKFD SALARRHIAR E.LRPEFYKD C.
CRF01 AE T EREVLMWKFD SALARKHIAR E.MHPEYYKD C.
CRF01 AE T EREVLMWKFD SALARKHVAR E.QHPEYYKD C.
CRF01 AE T EREVLIWKFD SSLARKHLAR E.LHPEYYKD C.
CRF02 AG_F DREVLVWRFD SSLARTHRAR E.LHPEYYKD C.
CRF02_AG_F DREVLVWRFD SSLARRHIAR E.RHPEFYKD C.
CRF02_AG_G DREVLVWRFD SSLAFTHRAR E.MHPEFYKD C.
CRF02_AG_N DREVLIWRFD SRLAFRHTAR E.LHPEYYKD C.
CRF02_AG_S DREVLVWRFD SRLAFTHKAR E.MHPEFYKD CX
CRF02_AG_S . DKEVLVWRFD SRLAFRHTAR E.LHPEYYKD C.
CRF03 AB R EKEVLMWKFD SRLALTHRAR E.LHPEFYKD C.
CRF03 AB R EKEVLMWKFD SRLALTHRAR E.LHPEFYKD C.
CRF04_cpx_ EREVLKWKFD SRLAYKHVAR E.LHPEFYKD C.
CRF04_cpx_ EREVLKWKFD SRLAFKHIAR E.LHPEFYKD C.
CRF04_cpx_
           EREVLKWKFD SLLAYRHMAR E.LHPEFYKD C.
CRF05_DF_B DREVLOWKFD SSLALRHIAR E.RHPEFYQD ..
CRF05_DF_B DGEVLRWKFD SSLALKHIAR E.RRPEFYQD ..
CRF06_cpx_ EREVLKWKFD SSLARRHIAR E.KHPEFYKD C.
CRF06_cpx_
           EGEVLMWKFD SSLARRHIAR E.LHPDFYKD C.
CRF06_cpx_
           EREVLMWKFD SSLARRHTAR E.MHPEFYKD C.
CRF06_cpx EXEVLMWKFD SSLARRHIAX E.XHPEFYKD C.
CRF11_cpx_
           EREVLKWVFD SSLARKHIAR E.LHPDFYKD ..
CRF11_cpx_ DREVLRWKFD SSLARRHIAR E.LHPDFYKD ..
D_CD_84ZRO EKEVLVWRFN SRLAFEHKAK E.KYPEYFKN C.
  D_CD_ELI ERQVLKWRFN SRLAFEHKAR E.MHPEFYKN ..
  D_CD_NDK ERQVLMWRFN SRLALEHKAR E.LHPEFYKD C.
D_UG_94UG1 EREVLVWRFN SRLAFEHKAK M.KHPEYYKD C.
F1_BE_VI85 DREVLRWKFD SSLALRHIAR E.RHPEFYQD ..
F1 BR 93BR DKEVLKWEFD SRLALRHIAR E.RHPEYYQD ..
           DREVLKWKFD SRLALKHIAR E.RHPEFYRD ..
F1 FI FIN9
F1 FR MP41 DREVLRWEFD SRLAFRHIAR E.KHPEFYQN ..
F2_CM MP25
           DKEVLKWQFD SRLALRHIAR E.RHPEYYKD ..
           EREVLVWKFD SRLALKHLAR E.KHPEYYKD C.
F2KU BE VI
G BE DRCBL
           DGEVLVWRFD SSLARRHLAR E.LHPEYYKD C.
          DREVLVWRFN SSLARRHLAR E.LHPEYYKD C.
G NG 92NG0
G_SE_SE616
           DREVLVWRFD SSLARRHIAR E.LHPEYYKD C.
H_BE_V1991
           EREVLMWKFD SRLALRHRAK E.LHPEFYKD C.
           EGEVLMWKFD SRLAFTHTAR E.KHPEFYKD C.
H_BE_VI997
           GREVLMWKFD SRLALTHLAR V.KHPEY.KD C.
H_CF_90CF0
J SE SE702
           EREVLKWKFD SSLARRHIAR E.LHPEFYKD C.
J_SE_SE788
           EREVLOWKFD SSLARRHIAR E.LHPEFYKD C.
K CD EQTB1
           HREVLKWKFD SSLARKHVAR E.MHPEYYKD ...
K CM MP535
           HREILMWKFD SSLARRHVAR E.LHPDYYKD ..
N CM YBF30
           HKEVLVWRFD SSLARRHVAR E.LHPEFYKN C.
           HKEILMWKFD RSLGNTHVAM ITHPELFQKD ...
O CM ANT70
           HGEILKWQFD RSLGLTHIAL QKHPELFPSN ..
O CM MVP51
O_SN_MP129 HGQILKWQFD RSLGSTHVAM VTNPELFNKD ..
O_SN_MP130 HKEMLKWQFD RSLGSTHVAL ITHPELFLKD ..
U_CD__83C EKEVLMWKFD SSLARRHLAR E.LHPEFYKD C.
```

Table 14. HIV Pol Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

Name:		Len:	1046	Check:	4376	Weight:	1.00
Name:		Len:	1046	Check:			
Name:		Len:	1046	Check:	8925	Weight:	
Name:		Len:	1046	Check:	1324	Weight:	
Name:	-	Len:	1046	Check:	935	Weight:	1.00
Name:	· · · · · -	Len:	1046	Check:	8131	Weight:	1.00
Name:		Len:	1046	Check:	579	Weight:	1.00
Name:	· —	Len:	1046	Check:	1975	Weight:	1.00
Name:		Len:	1046	Check:	216	Weight:	1.00
Name:	-	Len:	1046	Check:			
Name:		Len:	1046	Check:			
Name:		Len:	1046	Check:			1.00
Name:		Len:	1046	Check:	7093	Weight:	1.00
Name:		Len:	1046	Check:	2524	Weight:	1.00
Name:		Len:	1046	Check:	8279	J	
Name:		Len:	1046	Check:	3935	Weight:	1.00
Name:		Len:	1046	Check:			1.00
Name:		Len:	1046	Check:	728	Weight:	1.00
Name:		Len:	1046	Check:		Weight:	1.00
		Len:	1046	Check:			1.00
Name:		Len:	1046	Check:			1.00
Name:		Len:	1046	Check:			
Name:	· · · - · · ·	Len:	1046	Check:			
Name:		Len:	1046	Check:			1.00
Name:		Len:	1046	Check:	8244	Weight:	
Name:		Len:	1046	Check:		_	1.00
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Name:		Len:	1046	Check:		Weight:	1.00
Name:		Len:	1046	Check:		Weight:	1.00
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Name:		Len:	1046	Check:	7173	Weight:	1.00
Name:	_	Len:	1046	Check:	973	Weight:	1.00
Name:	96BW15B03	Len:	1046	Check:	5817	Weight:	1.00
Name:	96BW16_26	Len:	1046	Check:	5157	Weight:	1.00
Name:		Len:	1046	Check:	3303	Weight:	1.00
Name:	96BWMO1_5	Len: Len:	1046	Check:	1256	Weight:	1.00
Name:	96BWM03_2		1046	Check:	5593	Weight:	1.00
Name:	98BWMC12 2	Len: Len:	1046	Check:	3661	Weight:	1.00
Name:	98BWMC13_4	Len:	1046	Check:	7159	Weight:	1.00
Name:	98BWMC14_a	Len:	1046	Check:	3254	Weight:	1.00
Name:	98BWM014 1	Len:	1046 1046	Check:		Weight:	1.00
Name:	98BWM018_d	Len:		Check:	7680	Weight:	1.00
	98BWM036_a	Len:	1046	Check:	1619	Weight:	1.00
Name:		Len:	1046	Check:		Weight:	1.00
Name:		Len:	1046	Check:		Weight:	1.00
Name:		Len:	1046	Check:	5391	Weight:	1.00
Name:	_ ·		1046	Check:		Weight:	1.00
Name:		Len: Len:	1046			Weight:	1.00
Name:		Len:	1046 1046		4905	Weight:	1.00
	A2_CD_97CD	Len:	1046		1544	Weight:	1.00
Name:	A2_CY_94CY	Len:	1046	_	9703	Weight:	1.00
Name:		Len:	1046		3235	Weight:	1.00
Name:	A2G_CD_97C	Len:	1046		3776	Weight:	1.00
Name:	A BY 97BLO	Len:	1046		2059	Weight:	1.00
		Den:	7040	CHECK:	2724	Weight:	1.00

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Name: A_KE_Q23 A
                         Len:
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                                       Check: 1835 Weight:
                                                                1.00
Name: A SE SE659
                         Len:
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                                       Check: 647
                                                    Weight:
                                                               1.00
Name: A SE SE725
                         Len:
                                 1046
                                       Check: 263
                                                    Weight:
                                                               1.00
Name: A SE SE753
                         Len:
                                 1046
                                       Check: 2271
                                                     Weight:
                                                                1.00
Name: A SE SE853
                         Len:
                                 1046
                                       Check: 5036
                                                     Weight:
                                                                1.00
Name: A_SE_SE889
                         Len:
                                 1046
                                       Check: 8414
                                                     Weight:
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Name: A_SE_UGSE8
                         Len:
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                                       Check: 3268
                                                     Weight:
                                                                1.00
Name: A_UG_92UG0
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                                       Check: 2007
                                                     Weight:
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Name: A_UG_U455
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                                 1046
                                       Check: 2277
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Name: AC_IN 2130
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                                       Check: 5353
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Name: AC_RW_92RW
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                         Len:
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Name: AC_SE_SE94
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                                                     Weight:
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Name: ACD_SE_SE8
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                                 1046
                                       Check: 7281
                                                     Weight:
                                                                1.00
Name: ACG BE VI1
                         Len:
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                                       Check: 1400
                                                     Weight:
                                                                1.00
Name: AD SE SE69
                         Len:
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                                       Check: 4640
                                                     Weight:
                                                                1.00
Name: AD SE SE71
                         Len:
                                 1046
                                       Check: 1057
                                                     Weight:
                                                                1.00
Name: ADHK_NO 97
                         Len:
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                                       Check: 3502
                                                     Weight:
                                                                1.00
Name: ADK_CD_MAL
                         Len:
                                 1046
                                       Check: 2578
                                                     Weight:
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Name: AG_BE_VIll
                         Len:
                                 1046
                                       Check: 8416
                                                     Weight:
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Name: AG NG 92NG
                         Len:
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                                       Check: 9397
                                                     Weight:
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                                       Check: 9562
Name: AGHU GA VI
                         Len:
                                 1046
                                                     Weight:
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Name: AGU_CD Z32
                         Len:
                                 1046
                                       Check: 8398
                                                     Weight:
                                                                1.00
Name: AJ_BW_BW21
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                                 1046
                                       Check: 3451
                                                     Weight:
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Name: B AU VH AF
                         Len:
                                 1046
                                       Check: 2033
                                                     Weight:
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Name: B CN RL42
                         Len:
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                                       Check: 1369
                                                     Weight:
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Name: B DE D31 U
                                       Check: 4607
                         Len:
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                                                                1.00
Name: B DE HAN U
                                       Check: 1771
                         Len:
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                                                                1.00
Name: B_FR_HXB2_
                         Len:
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                                                     Weight:
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Name: B_GA_OYI_
                         Len:
                                 1046
                                       Check: 3682
                                                     Weight:
                                                                1.00
Name: B_GB_CAM1
                         Len:
                                 1046
                                       Check: 3161
                                                     Weight:
                                                                1.00
Name: B GB GB8 A
                         Len:
                                       Check: 6253
                                 1046
                                                     Weight:
                                                                1.00
Name: B GB MANC
                         Len:
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                                       Check: 7670
                                                     Weight:
                                                                1.00
Name: B_KR_WK_AF
                         Len:
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                                       Check: 8737
                                                     Weight:
                                                                1.00
Name: B_NL_3202A
                         Len:
                                 1046
                                       Check: 2083
                                                     Weight:
                                                                1.00
Name: B TW TWCYS
                         Len:
                                       Check: 3056
                                 1046
                                                     Weight:
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Name: B US BC LO
                         Len:
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                                       Check: 3160
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Name: B US DH123
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                                       Check: 1102
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                                                                1.00
Name: B_US_JRCSF
                         Len:
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                                       Check: 5571
                                                     Weight:
                                                                1.00
Name: B_US_MNCG_
                                       Check: 3988
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                                                     Weight:
                                                                1.00
Name: B_US_P896
                         Len:
                                1046
                                       Check: 2465
                                                     Weight:
                                                                1.00
Name: B_US_RF_M1
                         Len:
                                1046
                                       Check: 3672
                                                     Weight:
                                                                1.00
Name: B_US_SF2 K
                                       Check: 1754
                         Len:
                                 1046
                                                     Weight:
                                                                1.00
Name: B US WEAU1
                         Len:
                                1046
                                       Check: 2993
                                                     Weight:
                                                                1.00
Name: B US WR27
                                       Check: 4098
                         Len:
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                                                     Weight:
                                                                1.00
Name: B_US_YU2 M
                                       Check: 5564
                         Len:
                                1046
                                                     Weight:
                                                                1.00
Name: BF1 BR 93B
                         Len:
                                1046
                                       Check: 4182
                                                     Weight:
                                                                1.00
Name: C BR 92BR0
                         Len:
                                1046
                                       Check: 5481
                                                     Weight:
                                                                1.00
Name: C_BW_96BW0
                                       Check: 6833
                         Len:
                                1046
                                                     Weight:
                                                                1.00
Name: C_BW_96BW1
                         Len:
                                1046
                                       Check: 2166
                                                     Weight:
                                                                1.00
Name: C_BW_96BW1
                         Len:
                                1046
                                       Check: 5817
                                                     Weight:
                                                                1.00
Name: C_BW_96BW1
                         Len:
                                1046
                                       Check: 5157
                                                     Weight:
                                                                1.00
Name: C_ET_ETH22
Name: C_IN_93IN1
Name: C_IN_93IN9
                         Len:
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                                       Check: 3509
                                                     Weight:
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                                       Check: 5471
                         Len:
                                1046
                                                     Weight:
                                                                1.00
                         Len:
                                1046
                                       Check: 4102
                                                     Weight:
                                                                1.00
Name: C_IN_93IN9
                         Len:
                                1046
                                       Check: 3150
                                                     Weight:
                                                                1.00
Name: C_IN_94IN1
                         Len:
                                1046
                                       Check: 5157
                                                     Weight:
                                                                1.00
Name: C IN 95IN2
                         Len:
                                1046
                                       Check: 4641
                                                     Weight:
                                                                1.00
Name: CRF01 AE C
                         Len:
                                1046
                                       Check: 87 Weight:
                                                              1.00
Name: CRF01_AE C
                         Len:
                                1046
                                       Check: 3758
                                                    Weight:
                                                                1.00
Name: CRF01_AE_C
                                       Check: 2775 Weight:
                         Len:
                                1046
                                                                1.00
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Name: CRF01 AE T
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                                      Check: 7414
                                                   Weight:
                                                              1.00
 Name: CRF01_AE_T
                        Len:
                                1046
                                      Check: 7837
                                                   Weight:
                                                              1.00
 Name: CRF01 AE T
                        Len:
                                1046
                                      Check: 3529
                                                   Weight:
                                                              1.00
 Name: CRF01 AE T
                        Len:
                                1046
                                      Check: 7503
                                                   Weight:
                                                              1.00
 Name: CRF01 AE T
                        Len:
                                1046
                                      Check: 5730
                                                   Weight:
                                                              1.00
 Name: CRF02 AG F
                        Len:
                               1046
                                      Check: 9432
                                                   Weight:
                                                              1.00
 Name: CRF02 AG F
                        Len:
                               1046
                                      Check: 2064
                                                   Weight:
                                                              1.00
 Name: CRF02 AG G
                        Len:
                               1046
                                     Check: 9849
                                                   Weight:
                                                              1.00
 Name: CRF02 AG N
                        Len:
                                1046
                                     Check: 1793
                                                   Weight:
                                                              1.00
 Name: CRF02_AG_S
                        Len:
                                1046
                                     Check: 4817
                                                   Weight:
                                                              1.00
 Name: CRF02_AG_S
                        Len:
                                1046 Check: 1764
                                                   Weight:
                                                              1.00
 Name: CRF03_AB_R
                        Len:
                               1046 Check: 1695
                                                   Weight:
                                                              1.00
 Name: CRF03_AB_R
                        Len:
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                                     Check: 1425
                                                   Weight:
                                                              1.00
 Name: CRF04_cpx_
                        Len:
                               1046
                                     Check: 8496
                                                   Weight:
                                                              1.00
 Name: CRF04_cpx
                        Len:
                                1046
                                     Check: 2074 Weight:
                                                              1.00
 Name: CRF04 cpx
                        Len:
                                1046
                                     Check: 9245
                                                   Weight:
                                                              1.00
 Name: CRF05 DF B
                        Len:
                               1046
                                     Check: 62 Weight:
                                                           1.00
 Name: CRF05_DF B
                                     Check: 3427 Weight: 1.00
                        Len:
                               1046
Name: CRF06_cpx_
                                     Check: 142 Weight:
                        Len:
                               1046
                                                             1.00
 Name: CRF06_cpx
                               1046 Check: 6688 Weight:
                        Len:
                                                             1.00
Name: CRF06_cpx_
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Name: CRF06_cpx_
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                                                   Weight:
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Name: CRF11_cpx_
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Name: CRF11_cpx_
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                                     Check: 8466
                                                   Weight:
                                                              1.00
Name: D_CD_84ZR0
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                               1046
                                     Check: 515
                                                  Weight:
                                                            1.00
Name: D_CD_ELI K
                        Len:
                               1046
                                     Check: 2096
                                                   Weight:
                                                             1.00
 Name: D CD NDK M
                        Len:
                               1046
                                     Check: 3376
                                                   Weight:
                                                             1.00
 Name: D UG 94UG1
                                     Check: 3505
                        Len:
                               1046
                                                   Weight:
                                                             1.00
Name: F1 BE VI85
                        Len:
                                     Check: 3993
                               1046
                                                   Weight:
                                                              1.00
Name: F1_BR_93BR
                        Len:
                               1046
                                     Check: 2251
                                                   Weight:
                                                             1.00
 Name: F1_FI_FIN9
                        Len:
                               1046
                                     Check: 9772
                                                   Weight:
                                                             1.00
Name: F1_FR_MP41
                        Len:
                               1046
                                     Check: 1447
                                                   Weight:
                                                             1.00
Name: F2_CM_MP25
                        Len:
                               1046 Check: 2842 Weight:
                                                             1.00
Name: F2KU BE VI
                        Len:
                                     Check: 5026
                               1046
                                                   Weight:
                                                              1.00
                                     Check: 5377
Name: G BE DRCBL
                        Len:
                               1046
                                                   Weight:
                                                             1.00
Name: G_NG_92NG0
                        Len:
                               1046
                                     Check: 6000
                                                   Weight:
                                                             1.00
Name: G_SB_SE616
                        Len:
                               1046
                                     Check: 7901
                                                   Weight:
                                                             1.00
Name: H_BE VI991
                                     Check: 9107
                        Len:
                               1046
                                                   Weight:
                                                             1.00
Name: H BE VI997
                        Len:
                                     Check: 5776
                               1046
                                                   Weight:
                                                             1.00
Name: H CF 90CF0
                        Len:
                               1046
                                     Check: 9201
                                                   Weight:
                                                             1.00
Name: J SE SE702
                        Len:
                               1046
                                     Check: 9700
                                                   Weight:
                                                             1.00
Name: J_SE_SE788
                        Len:
                               1046
                                     Check: 8817
                                                   Weight:
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Name: K_CD_EQTB1
                        Len:
                               1046
                                     Check: 3723
                                                   Weight:
                                                             1.00
Name: K_CM_MP535
                        Len:
                               1046
                                     Check: 3729
                                                   Weight:
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Name: N CM YBF30
                                     Check: 3336
                        Len:
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                                                   Weight:
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Name: O CM ANT70
                        Len:
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                                     Check: 9461
                                                   Weight:
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Name: O_CM_MVP51
                        Len:
                               1046
                                     Check: 2986
                                                   Weight:
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Name: O_SN_99SE_
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                                     Check: 377
                                                  Weight:
                                                            1.00
Name: O_SN 99SE
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                                     Check: 9312
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                                                  Weight:
                                                             1.00
Name: U_CD___83C
                        Len:
                               1046
                                     Check: 1358
                                                  Weight:
                                                             1.00
//
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00BW0762_1
           FFRENLAFPQ G.EAREFPPE QT...... RANSPT SR....E
00BW0768 2
           FFRENLAFPQ .GEAGEFPSE ................QTRANSTT SR......K
           FFRENLAFPQ G.EAREFPPE QA...... RAISPT SR....E
00BW0874 2
00BW1471 2
           FFRENLAFSE G.EARELPSE Q...... ARAISPT SR.....E
00BW1616_2 FPRENLAFPQ G.KAGEFPPE QTRANSP....SSTSANSPT SR.....E
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00BW1686_8 FFRENLAFPQ G.EAREFPSE Q...... ....ARAISPT SR.....E
00BW1759_3
           FFRENLAFPQ .GEAREFPSE ...... ..QTRANSPT TR.....E
00BW1773_2
           FFRENLAFPQ G.EAREFPSE QTRAN..... SPT SR.....E
00BW1783 5
           FFRENLAFPE GGEAREFPAE QTSRE..... ..QTRANSPT SR.....E
           FFRENLAFPQ G.EAREFPSE QT...... RANSPT SR.....E
00BW1795 6
00BW1811 3
           FFRENLAFPQ G.EAREFPSE QARANSPTR. ....ANSPT SR.....E
00BW1859 5
           FFRENLAFPQ G.KAREFSPE QA...... RANSPT SR.....E
00BW1880 2
           FFRENLAFPQ G.EAREFPPE QT...... RADSPT SR....E
00BW1921_1 FFRENLAFPQ G.EAREFPSE Q...... ...ARANSST SR.....E
00BW2036_1 FFRENLAFQQ G.KAREFPSE QNSP......TRRANSPT SR.....E
00BW2063_6 FFRENLAFPQ G.EAREFPSE QT......RANSPT SR.....K
00BW2087_2 FFRENLAFPQ GGEAGEFPSE ................QTRANSPT SR......A
00BW2127_2
           FFGENLAFPQ G.EAREFPPE QARTNSP.....QAGAISPT SR.....E
           FFRENLAFQQ GEAREFPSE QTRTNSPTSR .EQTRANSPT SG.....E
00BW2128_3
           FFRETLAFQQ G.KARELPSE QDRANSPTR. .....ANSPT GR......Q
00BW2276_7
           FFRENLAFPQ G.EAREFPPK QARTNSP.....NSPT SR....E
00BW3819 3
           FFREDLAFPR R.KAREFPSE QNRAN..... SPTRANSPT SR.....B
00BW3842 8
00BW3871 3
           FFRENLAFPQ G.EAREFPSE Q...... TRANSPT SR.....K
           FFRENLAFPQ G.KAREFPSK QA..... EANSPT GR....E
00BW3876 9
           FFRENLAFPQ G.EAREFPSE QTRANSPT. . . . SRANSPT SR. . . . E
FFRENLAFPQ G.EAREFSSE . . . . Q. . . . ARANSPT SR. . . . E
00BW3886 8
00BW3891 6
00BW5031 1
           FFRENLAFQQ G.EARELPPE Q...TRTNS. ..PTNANSPT SR.....E
           FFRENLAFPQ G.KAREFPSE Q.....TR. ....AISPT SR.....E
 96BW01B21
           FFRENLAFPQ G.EAREFPSE Q...... TRANSPT SR.....E
  96BW0407
           FFRENLAFPQ G.EAREFPPE QIRASSPNS. .....TNSPT SR.....E
  96BW0502
 96BW06 J4
          FFRENLAFPQ RGEAREFPSE ...... ...QARANSPT SR.....E
 96BW11_06 FFRENLAFPQ G.EAREFPSE .............QTGANSPT SR.....E
  96BW1210 FFRENLAFPQ G.EAREFPSE QTRAIS.... PT SR.....E
 96BW15B03 FFREDLAFPQ G.KAREFPSE QN.........RANSPT SR....E
96BW16_26 FFRENLAFPQ .GEAREFPSE .........QTRANSPT SG.....E
 96BW17A09 FFRENLAFPQ GGEAREFPSE Q...... ARANSPT SR.....E
 96BWM01 5
           FFRENLAFPQ G.EAREFPSE QT......RANSPT SR.....N
           FFRENLAFPQ G.EAREFPPE QT...... RANSPT SR.....A
 96BWM03_2
           FFRETLAFPQ G.EAREFSSE QG...... RANSPT SR....E
98BWMC12 2
           FFRENLAFPQ G.EAREFPSE QT...... RANSPT SR.....K
98BWMC13 4
           FFRENLAFPQ G.EARELPSE Q...... TRTISPT SR.....E
98BWMC14_a
98BWM014_1
           FFRENLAFPQ RGEAGEFPSE ...... ..KTRANSPT SR....E
           FFRENLAFPQ G.EAGKFHSE QTSANSP... ..TSRANSPT SR.....E
98BWM018 d
          FFRENLAFPQ G.EAREFPPE QTRANSP.....TSRANSPT GR.....E
98BWM036_a
98BWMO37_d FFRENLAFPQ G.EAREFPSE K............TRANSPT GR.....E
99BW3932_1
           FFRENLAFQQ G.EAREFPPE QDSANSPTSR ELQDRANSPT SR.....E
99BW4642_4
           FFRENLAFPQ G.EAREFLPE QD........RANSPT SR.....E
99BW4745_8
           FFRENLAFQQ G.EAREFPSE QTRANSP... ...TRANSPT SR.....E
           FFRKNLAFQQ G.EAREFPSE QT...... RANSPT SR.....E
99BW4754_7
           FFREDLAFQQ R.EAREFPSE Q.TRANS... ..PTRANSPT SR.....E
99BWMC16 8
A2 CD 97CD
           FFRENLAFQQ R.EAREFSSE ..............QDRANSPT N........
           FFRENLAFQQ R.EARKFSSE ...... ..QNRANSPT SR.....E
A2_CY_94CY
A2D 97KR
           FFRENLAFPQ R.EAREFSSE ............QNRTNSPT SR......G
A2G CD 97C
           FFRENLAFQQ R.EAREFS.. ..... SEQDRANSPT RR.....E
          FFRKNLAFQQ R.EARKFSSE ..........QTRAISPT S.....RK
A BY 97BLO
           FFRENLAFQK G.EAREFSSE ............QTGTNSST S......RD
A KE Q23 A
A SE_SE659 FFRENLAFQQ R.EARKFSSE .............QTRANSPT S......RD
A_SE_SE725
          FFRENVAFQQ G.EARKFSSE ...............QTGANSPT S......RA
           FFRENLAFQQ G.EAGKFSSB ..............QTGANSPT S......RD
A_SE_SE753
           FFRENLAFQQ R.EARKFSSE ................QTRANSPT S......RD
A SE SE853
           FFRENLAFQQ G.EARKFSSE ...............QTGANSPT S......RD
A SE SE889
A SE UGSE8
          FFRENLAFPQ G.EAGKFSSE ............QTGAISPT S......RD
A_UG_92UG0 FFRENLAFQQ R.EARKFSSE ......QTRTNSPT SS.....RD
A_UG_U455_ FFRENLAFQQ G.EAREFSSE ..............QTRANSPT SR......N.
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AC_IN_2130	FFRENLAFPQ	G.EAREFPSE		QTRANSPA	SRE
AC_RW_92RW	FFRENLAFQQ	G.EARKFSPE	Q	TGANSPT	SRE
AC_SE_SE94		G.EARKFSSE	• • • • • • • • • • • • • • • • • • • •	QTGANSPT	SRD
ACD_SE_SE8		G. KAREFPSE			SRE
ACG_BE_VI1		G. EARKFSSE	• • • • • • • • • • • • • • • • • • • •		SRANSPTSRE
AD_SE_SE69		G. KAREFPSE	• • • • • • • • •	QTRANSPS	SRE
AD_SE_SE71 ADHK NO 97		G.EARKFSSE	• • • • • • • • • • • • • • • • • • • •		SRN.
		R. KARELSSE	• • • • • • • • • • • • • • • • • • • •	QTGAISPT	$\mathtt{SR}.\dots.\mathtt{E}$
ADK_CD_MAL		G. KAREFPSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	$\mathtt{SR}.\dots.\mathtt{E}$
AG_BE_VI11 AG NG 92NG		G. EARKFSSE	• • • • • • • • • • • • • • • • • • • •		$\texttt{S}.\dots\texttt{RE}$
AG_NG_92NG AGHU_GA VI		G.EAREFS	• • • • • • • • • • • • • • • • • • • •		$\mathtt{RR}.\dots.\mathtt{E}$
AGU_CD Z32		G.EAREFS G.EAREFSSE	• • • • • • • • • • • • • • • • • • • •	PEQTRANSPT	$\mathtt{SR}.\dots.\mathtt{E}$
AJ BW BW21			• • • • • • • • • • • • • • • • • • • •	. QTRANSPT	$\mathtt{RR}.\dots.\mathtt{E}$
B_AU_VH_AF		G.KAREFSPE G.KARELSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	$\mathtt{SR}.\dots.\mathtt{E}$
B_CN_RL42		G. KARELSSE G. KARELSSE	• • • • • • • • • • • • • • • • • • • •		$\mathtt{RR}.\dots.\mathtt{E}$
B DE D31 U		G. KAREESSE G. KAREESSA	• • • • • • • • • • • • • • • • • • • •		RGE
B DE HAN U		G. EARKFSSE		QTRANSPT	RRE
B FR HXB2		G. KAREFSSE	• • • • • • • • • • • • • • • • • • • •	OTRANSPT	RRE
B GA OYI		G. KAREFSSE	• • • • • • • • • • • • • • • • • • • •		RRE
B GB CAM1		G.EAREFSSE	••••••		SRE
B GB GB8 A		G. KAREFSPE	OTDANG		RRE
B GB MANC			QIRANS	OTRADSPT	RRE
B KR WK AF		G. KAREFPSE		OTRANSPT	RGE
B NL 3202A		G. KAREFSSE			RRE
B TW TWCYS		G. KARKFSSE			RRE
B US BC LO	FFREDLAFPO	G. KAREFSSE	• • • • • • • • • • • • • • • • • • • •		RGE
B US DH123			• • • • • • • • • • • • • • • • • • • •		RRE
B_US_JRCSF		G. KAREFPSE			RRE
B_US_MNCG_		G.KAEFS.SE			RRE
B_US_P896		G.KAREFSSE		OTDANSPI	RRE
B_US_RF_M1		G.KARELSSE	• • • • • • • • • • • • • • • • • • • •		RRE
B_US_SF2_K		G. KAREFSSE	• • • • • • • • • • •	OTRANSPT	RRE
B_US_WEAU1		G.KAREFSSE			RRE
B_US_WR27_		X. KARXFPSE	• • • • • • • • • •	QTRAISPT	CD E
B_US_YU2_M	FFRBDLAFPQ	G. KARKFSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPI	PR F
BF1_BR_93B	FFRENLAFPQ	G.KAREFPSE	• • • • • • • • • •	~	SP F
C_BR_92BR0	FFRENLAFPQ	.GEARKSSSE		. ONRANCOT	DD E
C_BW_96BW0	FFRENLAFPQ	G.EAREFPSE	Q	TRANSPT	SRE
C_BW_96BW1	FFRENLAFPQ	G.EAREFPSE		OTGANSPT	QD V
C_BW_96BW1	FFRENLAFPQ	G.EAREFPSB	OTRAIS	סידים	CD E
C_BW_96BW1	FFREDLAFPQ	G.KAREFPSE	QN	RANSPT	SR
C_ET_ETH22	FFRETLAFQQ	G.KAREFPSE	QTRANSPTRE	S.QTRANSPT	TRE
C_IN_93IN1	FFRENLAFPQ	G.EAREFPPE		OTGANSPT	SR E
C_IN_93IN9	FFRENLAFPQ	G.EAREFPPE		QTRADSPT	SRE
C_IN_93IN9	KAKENPALLO	G.EAREFPSE	QTRANSPSS.	OTRANSPS	SR E
C_IN_94IN1	FFRENLAFPQ	G.EAREFPPE		. OTRANSPT	SP F
C_IN_95IN2	FFRENLAFPQ	G.EAREFPP.	• • • • • • • • • • • • • • • • • • • •	. ETRANSST	SRE
CRF01_AE_C	FFRENLASQQ	G.EAREFSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	SRE.
CRF01_AE_C	FFRENLAFQQ	G.EARKFPSE			NGE.
CRF01_AE_C		G.EAREFSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	SRE.
CRF01_AE_T CRF01 AE T	FFREILAFQQ	G. KAGKFSSE		QTRANSPA	SR
	CEREMIA POO	R. KAGEFSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	SR
CRF01_AE_T	PEDENTAGO	G. KAREFSSE	• • • • • • • • • • • • • • • • • • • •	QTGANSSA	SRK.
CRF01_AE_T CRF01_AE_T	EEDEMI APOS	G. KAGKFSSE	• • • • • • • • • • • • • • • • • • • •	QTRANSPT	SRE.
CRF01_AE_T	EPPENT APOS	G. KAGEFSSE	• • • • • • • • • •	QTRANSPT	SRK.
CRF01_AE_1 CRF02 AG F	EEDENII NEOO	G. KAGKESSE	• • • • • • • • • • • •	QTRTNSPT	SRK.
CRF02_AG_F	FREDENIARQQ	G. BARKESSK	• • • • • • • • • • • • • • • • • • • •	QTGTNSPT	SRE
CRF02 AG G	FERENIARQQ	D PARRESSK	• • • • • • • • • • • • • • • • • • • •	QTGTNSPT	SRE
	r e verativit 60	K.EAKELSSE	• • • • • • • • • •	QTGAISPT	GRE

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FFRENLAFQQ G.EARKFSSE ...............QTGTNSST S......RE
CRF02 AG N
           FFRENLAFQQ G.EARKFSSE ..............QTGTNSPA S......RE
CRF02 AG S
           FFRENLAFQQ G.EARKLSSE ..........QTGTNSPT S.....RE
CRF02 AG S
           FFRENLAFQQ R.EARKFSSE .............QTRAISPT S......RK
CRF03_AB_R
           FFRENLAFQQ R.BARKFSSE .........QTRAISPT S.....RK
CRF03 AB R
CRF04_cpx_
           FFRENVAFQQ R.EARKFSSE ...... ...QARANSPA RG.....M
           FFRENVAFQQ R.KAGEFSSE ...... ...QARANSPT RR.....E
CRF04 cpx
           FFRENVAFQQ G.EARKFSSE ...... QDRANSPA RR.....E
CRF04 cpx
CRF05 DF B
           FFRESLAFPQ G.EARELPPE ..... ..QTGALSPA SR.....E
CRF05 DF B
           FFRESLAFPQ G.KAREFPPE ..... ...QARTLSPT SR....E
CRF06_cpx_
           FFRENLAFQQ G.EAREFS.. ..... SEQARANSPT HR.....E
CRF06_cpx_
           FFREDLAFQQ G.EARKFS...... SEQARANSPT RG.....E
CRF06_cpx_
           FFRENLAFQQ G.EAGELS...... SEQARANSPT RR....E
FFRENLAFPQ G.EAREFSPE QAR..... TEQARTLSPT CR.....E
CRF06_cpx_
           FFRENLAFQQ R.KARELSPE ...... ..QTRANSPT SR.....E
CRF11_cpx_
           FFRENLAFQQ G.EAREFPTE ...... QARANSPT SR.....E
CRF11_cpx_
           FFRENLAFPQ G.KAGELSSE ...... ..QTRANSPT S.....R
D CD 84ZRO
           FFRENLAFPQ G.KAGELSPK ...... ..QTRANSPT SR.....E
D CD ELI K
D CD NDK M
           FFREDLAFPQ G.KAGEFSSE ...... ..QTRANSPT SR.....E
           FFRENLAFPQ W.KAREFPSE QT...... ..PSRANSPT SR.....D
D UG 94UG1
           FFRENLAFQQ G.EARKFPSE ...... ..QTRANSPT SR.....E
F1 BE VI85
           FFRENLAFQQ G.EARKLHPE ..... ...QARAVSPA SR.....E
F1_BR_93BR
           FFRENLAFQQ G.EARKFPS. ..... ETRANSPA SR.... E
F1_FI FIN9
           FFRENLAFQQ G.EARKFSSE ..... ... ... QARANSPA SG.....E
Fl_FR_MP41
           FFRENVAFQQ G.EARKFSSE ...... ...QTRANSPA SR.....E
F2 CM MP25
           FFRENLAFQQ R.EAGKFSSE ...... ..QTRANSPT SR.....E
F2KU BE VI
           FFRENLAFQQ G.EAREFP...... SEQARANSPT RR.....E
G BE DRCBL
           FFRENLAFQQ G.EARKLS...... PEQDRANSPT SR.....E
G_NG 92NG0
          FFRENLAFQQ G.EAREFS...... SEQDRTNSPT CR.....K
G SE SE616
H BE VI991
          FFRENLAFQQ G.KAREFP...... PEEARANSPT SR.....E
          FFRENLAFQQ R.EARKFS..... PEQARANSPT SR....E
H BE VI997
H_CF_90CF0 FFRENLAFQQ R.EARKFS... PEQARTNSPT SR...E
J_SE_SE702 FFREDLAFQQ R.EAREFSPE ... QTRANSPT SR...E
J_SE_SE788 FFREDLAFQQ R.EARELSPE ....... ..QTRANSPT SR.....E
K_CD_EQTB1 FFREVLASQQ R.EARKFSSE ......QTRANSPT SR....E
K_CM_MP535 FFRENLAFPQ G.EAREFSSE .....QTRANSPT SR....E
          FFREELVSLQ R.ETRKLPPD NN...... ..KERAHSPA TR.....E
N CM YBF30
O CM ANT70
          FFRQILASGG H.EARQLCAE T...... ...STPISPT DG......G
          FFREVLASGG H.EARQLCAE T..........SVPISPT NG......G
O CM MVP51
          FFREILASGG H.EARQLCAE T...... SVPISPT DD......G
O_SN_99SE_
          FFREILASGG H.EARQLCTE T...... ....SVPISPT DD......G
O SN 99SE
          FFRENLAFQQ G.EAREFSSE ...... ..QTRANSPT SR.....E
U CD 83C
          LQVR..... GTLNFPQITL
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          LQVRG..... GTLNCPQITL
00BW0768_2
          PQARAISPTS REPOVREDN. ....SRFEAG VEREG..... TLNFPQITL
00BW0874_2
00BW1471 2
          LQVR........GDN.....PRSEAG AERQG......TLNLPQITL
          LQVR..... GTLNFPQITL
00BW1616 2
00BW1686_8 LQVR..... GDN. ...PRSEAG AERQ..... GTLNLPQITL
00BW1759_3 LOVRG..... .NN. .... PRSEAG AERQ..... GNLNFPQITL
00BW1773_2 LQVR..... GDN. ....PRSEAG AERQ..... GTLNFPQ1TL
00BW1783_5 LQVR..... GDN. ....PCSEAG DERQ..... GTFNFPQITL
00BW1795_6 LQVR..... .GDN. ....PLSEAG AERQ..... GTLNFPQITL
00BW1859 5 LQVR..... GDD. ...PRSEAG AERQ..... GTLNFPQITL
00BW1880_2 LQVR..... .GDN. ....PRSEAG AEGQ..... GTLNFPQITL
00BW1921_1 LQVR......GDN.....PCSEAG AERQG..... TLNFPQITL
00BW2036_1 LQVR..... GDN. ....PRSEAG AERQ..... GTLNFPQITL
00BW2063_6 L.R......GDN....PCSEAG DERQ..... GTLNFPQITP
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NSPTSREL....QVRGDN. ....PSIKAG PERQ..... GALNFPQITL
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00BW2127 2
          LQVR..... . . . . . . GDN. . . . . PRSEAG AERQG.... . . SLNFPQITL
          LQVR..... GTLNFPQITL
00BW2128 3
          LQVR..... .....GDN. ....PRAEAG AERQG..... .TLNFPQITL
00BW2276 7
          LQVR.....GDN...PRSEAG DERQG....ALNFPQITL LQVR....GDN...PRSEAG AERQGT.LQ GTLNFPQITL
00BW3819 3
00BW3842 8
          LQVR..... GTLNFPQITL
00BW3871 3
00BW3876_9
          LQVR..... GTLNFPQITL
00BW3886_8
          LQVR..... .....GDN. ....PRSEAG AERQG..... .SLNFPQITL
00BW3891_6
          LQVR..... GDN. ....PRSEAG AERQG.... TLNFPQITL
          LQVR..... .....GDN. ....PRSETG AEGQG.... .TFNFPQITL
00BW3970_2
00BW5031_1
          LQVR..... .....CDN. ....PRSEAG DEREG.... .TLNFPQITL
          LQVR..... GDN. ....PRSEAG AEGQG.... ALNLPQITL
 96BW01B21
  96BW0407
          LQVR..... .....GDN. ....PRSETR VEGQG..... .NFNFPQITL
          96BW0502
 96BW06 J4
 96BW11 06
          LQVR.....GDN....PCSEAG AEGQG.... TTFSFPQITL
  96BW1210
 96BW15B03
          LQVR..... GTLNFPQITL
          LQVW..... GTFNFPQITL
 96BW16 26
          LQVR..... GDN. ....PRSEAG AERQG.... .TLNFLQITL
 96BW17A09
          L..R..... GDN. .... PCSEAG DERQGT..LQ GALNFPQITL
 96BWM01 5
          LQAR..... TNSP. ....TSREAG VEGQG..... .TLNFPQITL
 96BWM03 2
98BWMC12 2
          P............QARGDN.....TRFEAG DEGQG.......TLNFPQITL
98BWMC13 4
          P..R..... GDN. ....PCSEAG AERQ..... GTLNLPQITL
          LQVR..... GTLNFPQITL
98BWMC14 a
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98BWM014 1
          LQVR......GDN....PCSEAG AERQGS....TLNFPQITL
98BWM018 d
          LQVR......GDK....PRSEAG AEGQG.....TLNFPQITL
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98BWM037_d
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          LQVR..... GTPNFPQITL
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A2 CD 97CD
          ...GGR.... DN. ....LLAEAG E..QG...AV HPCNFPQITL
A2_CY_94CY
          LENGGR.... DN. ....LLPEAG TGDQG...TI QSCNFPQITL
          LWNGGG....DN....PLAEAG AEKQG...TT HSCNFPQITL
A2D 97KR
          PRVRR..... GDS. ....LLPEAG DEG...KGAV YPCNFPQITL
A2G CD 97C
          LD.GGR.....DN....PLPETG TERQG...TV SSFNFPQITL
A BY 97BL0
          LWDGGR.....DS. ....LPSEAG AERQGT..G. PTLSFPQITL
A_KE_Q23_A
A SE SE659
          PWDRRR.... .....DS. ....LPSETG ADP..... .TFSFPQITL
A SE SE725
          FWDGGR.... DS. ....LPSEAG AERQGT..E. LTFSFPQITL
          LWNEGR......DS. ....LPSEAG AEG..T..R. PTFSFPQITL
A SE SE753
A SE SE853
          LWDGGS.....DN. ....LPSEAG AERQGT..G. PTLSFPQITL
A SE SE889
          LWDGGR.....DN. ....LPSEAG EERQGV..GG TTLNFPQITF
          ..DGGR.... .....DS. ....LPSEAG AKQP..... .TFSFPQITL
A SE UGSE8
A UG 92UG0
          LWDEGR.... DS. ....LPSEAG AERQGP..E. PTFSFPQITL
A UG U455
          LWDGGK.....DD. ....LPCETG AERQ....GT DSFSFPQITL
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AC_IN_2130
AC_RW_92RW
          LWNGG..... .TFNFPQITL
AC"SE SE94
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ACD_SE SE8
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          LWEGGR.... DR. ....LLPEAG TEGQG...TI SSFNFPQITL
AD SE SE69
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ADHK NO 97
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ADK CD MAL
AG_BE VI11
          LRVRR..... GDS. ....PFPEAG AEG...KGIT SIN.LPQITL
AG NG 92NG
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ACUIT CA UT	t nunn	67.0			
AGHU_GA_VI		·····GDS.	····PLPEAG	AKGKGA	VSFNLPQITL
AGU_CD_Z32		GDN.	····LLSEAG	TEGQGTI	PSFSFPQITL
AJ_BW_BW21		GDS.	PLPEAG	GEGQGT	VSFNFPQITL
B_AU_VH_AF		DNN.	···.SLSEAG	ADRQGT	VSFSFPQITL
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B_DE_D31_U		DSN.	SLSEAG	ADRQGT	VSFSFPOITL
B_DE_HAN_U	LQVWG	SNS.	SLSEAG	ADRQGT	VSLSLPOTTI.
B_FR_HXB2_	LQVWGR	DNN.	SPSEAG	ADRQGT	VSPNFPOVTI.
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B GB CAM1	LQVWGR	ENN.	SLSEAG	ADRQGT	VSESEDOTTE
B GB GB8 A	LQVRGR	DNN.	SLITETG	ADKQGT	VOUSTPOINT
B GB MANC		DNN.	SCSEAG	TDRQGT	VOICEPORM
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B NL 3202A		DNN	CICEAG	ANKQGT	VSFSFPQITL
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B US BC LO		DNN.	CDCEAG	ADRQGP	VSFSFPRITL
B US DH123		DSN.	SPSEAG	AGRQGN	VSLSFPQITL
B_US_JRCSF			SLSEAG	AEGT	ISLSLPQITL
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B_US_MNCG_		DNN.	SLSEAG	EEAGDDRQGP	VSFSFPQITL
B_US_P896_		DNN.	SLSEAG	ADRQGT	VSLSFPQITL
B_US_RF_M1		DN	SLSEAG	EDRQGT	VSFSFPQITL
B_US_SF2_K		ENN.	SLSEAG	ADRQGT	VSFNFPQITL
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C_BW_96BW1	LRG	NN.	PCSEAG	DERQ	GTLNFPOITI.
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C_BW_96BW1	LQVR	GDN.	PRSEAG	AERQ	GTINEPOITI.
C_ET_ETH22	LQVR	GSN.	TFSEAG	AERQG	SINFPOITI
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C_IN_93IN9		GDT.	PSSKAG	AERQG	TIMPPOTTI
C IN 93IN9		GDN.	PRSEAG	AKRQG	TIMEPOTE
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CRF01 AE T		DN.	LITERG	AERQGTS	SSFSFPQITL
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CRF01 AE T			CONTRACTO	AERQGTP	SSFNFPQITL
CRF01_AE_I	I CDCCB	DNG	GRUNLLTEAG	AERQGTS	SSFSFPQITL
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	LUDGGR	DN.	LPSEAG	SEGPGTI	SSLSFPQITL
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CRF02_AG_S	PWDRGR	DN.	· · · · LLSEAG	TGGQGTI	SSLSFPQITL
CRF02_AG_S	LWDGGR	DN.	LLPEAG	TGGQGTI	PSFNFPQ1TL
CRF03_AB_R	LWDGGR	DN.	· · · · PLPETG	TEGOG TA	SSENEPOITI.
CRF03_AB_R	LWDGGR	DN.	· · · · PLPETG	TEROGTA	SSENI POITI.
CRF04_cpx_	LREERG	DN	LLSBAG	TEGOGT	ISENFPOITI.
CRF04_cpx_	LRDERG	DN	LLSEAG	TEGOGT	ISENFPOITE
CRF04_cpx_	LRDERG	DN	LLSEAG	TEGOGT	ISHNEPOTTI.
CRF05_DF_B	LQVWGG	DS	LLSEAG	AEGRGTV	PSLSFPOITI.
CRF05_DF_B	LRVWRG	DN	· · · · PLAEAG	AEG RGEV	PSLSEPOTTE
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CRF11 cpx
D CD 84ZRO
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D CD ELI K
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D UG_94UG1 LRIRGG.....DN.....TSSETG AER....QGT VSFNLPQITL
          LRVQRG.... DN.. ....PLSEAG AERR...GTV PSLSFPQITL
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          PRDQRR.... GTV PSLSFPQITL
F1 FI FIN9
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F1 FR MP41
F2 CM MP25
          LRVRGG.....DS......SLPEAG AERQG...TG SSLDFPQITL
F2KU BE VI
          LRVWGG.... DK.. ....PLSEAG DERQG...TG ASFNLPQITL
G BE DRCBL
          LRVRG..... GDS. ....PLPEAG AEG...KGT1 S.SIFPQITL
G NG 92NG0
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G SE SE616
          PRVRR..... GDS. ....PLPEAG DEG...KGAI S...LPQITL
H BE VI991
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K CM MP535
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N CM YBF30
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O CM MVP51
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O SN 99SE
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CRF01 AE T
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ACD SE SE8
ACG BE VI1
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C BW 96BW1
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           SAGERIIDII ATDIQTKELQ KQITKIQNFR VYYRDNRDPI WKGPAKLLWK
B US JRCSF
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B US P896
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B US RF M1
B_US_SF2_K
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B_US_WEAU1
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B_US_WR27
B US YU2 M
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BF1 BR 93B
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C BR 92BR0
C BW 96BW0
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C BW 96BW1
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C_BW_96BW1
C_ET_ETH22
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D CD NDK M
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C_BW_96BW0 GE.GAVVIQD NSDIKVVPRR KVKIIRDYGK QMAGADCVAG RQDED.
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  IN 93 IN1
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CRF02_AG_N GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
CRF02_AG_S GE.GAVVIQD NSDIKVVPRR KVKIVRDYGK QMAGDDCVAG RQDED.
           GE.GAVVIQD NSDIKVVPRR KTKILRDYGK QMAGDDCVAG GQNED.
CRF02_AG_S
CRF03_AB_R GE.GAVVIQD NNDIKVVPRR KAKIIRDYGK QMAGDDCVAS RQDED.
CRF03_AB_R GE.GAVVIQD NNDIKVVPRR KAKIIRDYGK QMAGDDCVAS RQDED.
           GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGNDCVAG RQDED.
CRF04_cpx_
           GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
CRF04_cpx_
CRF04_cpx_
           GE.GAVVIQD NSDIKVVPRK KAKIIRDYGK QMAGDDCVAG RQDED.
CRF05_DF_B GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
CRF05_DF_B GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
           GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
CRF06_cpx_
           GE.GAVVIQD NSEIKVVPRR KAKIIKDYGK QMAGDDCVAG RQDED.
CRF06_cpx_
           GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
CRF06_cpx_
CRF06_cpx GE.GAVVIQD NSEIKVVPRR KAKIIRDIGK QMAGDDCVAG RQDED.

CRF11_cpx GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
            GE.GAVVIQD NSDIKVVPRR KAKIIRDYGK QMAGDDCVAS RQDED.
D_CD_84ZR0
D_CD_ELI_K GE.GAVVIQD KSDIKVVPRR KVKIIRDYGK QMAGDDCVAS RQDED.
           GE.GAVVIQD NSDIKVVPRR KVKIIRDYGK QMAGDDCVAS RQDED.
D CD NDK M
            GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAS RQDED.
D_UG 94UG1
PI_BE_VI85 GE.GAVVIQD NSEIKIVPRR KAKIIRDYGK QMAVDDCVAG RQDED.
F1_BR_93BR GE.GAVVIQD NSBIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
           GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
F1_FI_FIN9
            GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
F1_FR_MP41
            GE.GAVVIQD NNEIKVIPRR KAKIIRDYGK QMAGDDCVAG RQDED.
F2 CM MP25
F2KU_BE_VI GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
G_BE_DRCBL GE.GAVVIQD NNEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
G_NG_92NG0 GE.GAVVIQD NNBIKVVPRR KAKILKDYGK QMAGGDCVAG RQDED.
G_SE_SE616 GE.GAVVIQD NNEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
H_BE_VI991 GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
H_BE_VI997 GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
H_CF_90CF0 GE.GAVVIQD NSEIKVVPRR EAKIIRDYGK QMAGDDCVAS RQDED.
J_SE_SE702 GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
J_SE_SE788 GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
K_CD_EQTB1 GE.GAVVIN. .SEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
           GE.GAVVIQD NSEIKVVPRR KAKIIRDYGK QMAGDDCVAG RQDED.
K CM MP535
N CM YBF30
           GE.GAVVIQD NGDIKVVPRR KAKIIRDYGK QMAGDGCVAS GQDENQ
O_CM_ANT70
           GE.GAVVIQD KGDIKVVPRR KAKIIREYGK QMAGTDSMAS GQTESE
O_CM_MVP51
           GE.GAVVIQD KGDIKVVPRR KAKIIRDYGK QMAGTDSMAN RQTESE
O_SN_99SE_
           GE.GAVVIQD KGDIKVVPRR KAKIIRHYGK QMAGTDSMAS GQTESE
```

EDPSEDES DECEDE

O_SN_99SE_ GE.GAVVIQD KGDIKVVPRR KAKIIRHYGK QMAGTDSMAS GQTESE U_CD__83C GE.GAVVIQD NSBIKVVPRR KAKIIRDYGK QMAGDDCVAS RQDEN.

Table 15. HIV Rev Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

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Name	· — ·	Len:	129	Check: 5102	Weight:	1.00
Name		Len:	129	Check: 5815	Weight:	1.00
Name		Len:	129	Check: 4144	Weight:	1.00
Name		Len:	129	Check: 5298	Weight:	1.00
Name		Len:	129	Check: 3871	Weight:	1.00
Name		Len:	129	Check: 4976	Weight:	1.00
Name:	·	Len:	129	Check: 5775	Weight:	1.00
Name	: 00BW1783_5	Len:	129	Check: 6142	Weight:	1.00
Name:		Len:	129	Check: 5055	Weight:	1.00
Name:	: 00BW1811_3	Len:	129	Check: 5804	Weight:	1.00
Name:		Len:	129	Check: 5252	Weight:	1.00
Name:		Len:	129	Check: 4995	Weight:	1.00
Name:	: 00BW1921_1	Len:	129	Check: 6482	Weight:	1.00
Name:		Len:	129	Check: 4770	Weight:	1.00
Name:		Len:	129	Check: 5384	Weight:	1.00
Name:	: 00BW2087_2	Len:	129	Check: 4848	Weight:	1.00
Name:	00BW2127_2	Len:	129	Check: 5783	Weight:	1.00
Name:	00BW2276_7	Len:	129	Check: 5364	Weight:	1.00
Name:	00BW3819_3	Len:	129	Check: 5712	Weight:	1.00
Name:	00BW3842_8	Len:	129	Check: 5586	Weight:	1.00
Name:	00BW3871_3	Len:	129	Check: 5299	Weight:	1.00
Name:	00BW3876_9	Len:	129	Check: 4423	Weight:	1.00
Name:	00BW3886_8	Len:	129	Check: 5415	Weight:	1.00
Name:	00BW3891_6	Len:	129	Check: 5426	Weight:	1.00
Name:	00BW3970 2	Len:	129	Check: 2613	Weight:	
Name:	00BW5031 <u>1</u>		129	Check: 4597	Weight:	1.00
Name:	96BW01B21	Len:	129	Check: 5653	Weight:	1.00
Name:	96BW0407	Len:	129	Check: 4310	Weight:	
Name:	96BW0502	Len:	129	Check: 4675	Weight:	1.00
Name:	96BW06_J4	Len:	129	Check: 5079	Weight:	1.00
Name:		Len:	129	Check: 5939	Weight:	1.00
Name:	96BW1210	Len:	129	Check: 5666	Weight:	1.00
Name:	96BW15B03	Len:	129	Check: 5102	Weight:	1.00
Name:	96BW16_26	Len:	129	Check: 5675	Weight:	1.00
Name:		Len:	129	Check: 2825	Weight:	1.00
Name:	96BWMO1 5	Len:	129	Check: 5636	Weight:	1.00
Name:	96BWMO3_2	Len:	129	Check: 6552	Weight:	1.00
Name:		Len:	129	Check: 3043	Weight:	1.00
Name:	98BWMC13 4	Len:	129	Check: 5518	Weight:	1.'00
Name:	98BWMC14_a	Len:	129	Check: 4358	Weight:	1.00
Name:	98BWM014_1	Len:	129	Check: 7531	Weight:	1.00
Name:	98BWM018_d	Len:	129	Check: 5291	Weight:	1.00
Name:	98BWMO36 a	Len:	129	Check: 6801	Weight:	1.00
Name:	98BWM037 d	Len:	129	Check: 4790	Weight:	1.00
Name:	_	Len:	129	Check: 5736	Weight:	1.00
Name:	99BW4642 4	Len:	129	Check: 6464	Weight:	1.00
Name:		Len:	129	Check: 6181	Weight:	1.00
Name:		Len:	129	Check: 5182	_	1.00
Name:		Len:	129	Check: 4245	Weight:	1.00
Name:		Len:	129	Check: 2625	Weight:	1.00
Name:		Len:	129	Check: 2625	Weight:	1.00
Name:		Len:	129	Check: 4114	Weight: Weight:	1.00
Name:	A2G CD 97C	Len:	129	Check: 4114	-	1.00
Name:	A_BY_97BL0	Len:	129	Check: 1115	Weight:	1.00
Name:		Len:	129	Check: 2684	Weight:	1.00
		-014.	~~,	ccn. 2004	Weight:	1.00

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                                                    Weight:
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 Name: A_SE_SE725
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                         ·Len:
                                 129
                                                    Weight:
                                                               1.00
 Name: A_SE_SE753
                         Len:
                                 129
                                       Check: 3636
                                                    Weight:
                                                               1.00
 Name: A_SE_SE853
                         Len:
                                 129
                                      Check: 1862
                                                    Weight:
                                                               1.00
 Name: A_SE SE889
                         Len:
                                 129
                                      Check: 2798
                                                    Weight:
                                                               1.00
 Name: A SE UGSE8
                         Len:
                                 129
                                      Check: 6865
                                                    Weight:
                                                               1.00
 Name: A_UG_92UG0
                                      Check: 4427
                         Len:
                                 129
                                                    Weight:
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 Name: A_UG_U455
                         Len:
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                                      Check: 3229
                                                    Weight:
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                                      Check: 5110
                                                    Weight:
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 Name: AC RW 92RW
                         Len:
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                                      Check: 5015
                                                    Weight:
                                                               1.00
 Name: AC_SE_SE94
                         Len:
                                 129
                                      Check: 7976
                                                    Weight:
                                                               1.00
 Name: ACD_SE_SE8
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                                      Check: 2296
                                                    Weight:
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 Name: ACG_BE_VI1
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 Name: AD SE SE69
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Name: AD SE SE71
                         Len:
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Name: ADHK NO 97
                         Len:
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                                      Check: 1890
                                                    Weight:
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Name: ADK CD MAL
                         Len:
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                                      Check: 5260
                                                    Weight:
                                                               1.00
Name: AG BE VI11
                                      Check: 4003
                         Len:
                                 129
                                                    Weight:
                                                               1.00
Name: AG NG 92NG
                         Len:
                                 129
                                      Check: 5027
                                                    Weight:
                                                               1.00
Name: AGHU GA VI
                         Len:
                                 129
                                      Check: 1978
                                                    Weight:
                                                               1.00
Name: AGU CD Z32
                         Len:
                                 129
                                      Check: 1958
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Name: AJ BW BW21
                                      Check: 2263
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Name: B_AU_VH_AF
                         Len:
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                                                    Weight:
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Name: B_CN_RL42_
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Name: B DE D31 U
                         Len:
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                                                    Weight:
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Name: B DE HAN U
                         Len:
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                                      Check: 4550
                                                    Weight:
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Name: B_FR_HXB2
                                      Check: 3649
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Name: B_GA_OYI M
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                         Len:
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                                                               1.00
Name: B GB CAM1
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Name: B GB GB8 A
                         Len:
                                 129
                                      Check: 3083
                                                    Weight:
                                                               1.00
Name: B_GB_MANC
                         Len:
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                                      Check: 5502
                                                    Weight:
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Name: B_KR_WK_AF .
                         Len:
                                 129
                                      Check: 4156
                                                    Weight:
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Name: B_NL_3202A
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Name: B_TW_TWCYS
                         Len:
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Name: B_US_BC_L0
                         Len:
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                                      Check: 4674
                                                    Weight:
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Name: B US DH123
                         Len:
                                129
                                      Check: 4202
                                                    Weight:
                                                               1.00
Name: B_US_JRCSF
                         Len:
                                129
                                      Check: 3217
                                                    Weight:
                                                               1.00
Name: B_US MNCG
                                      Check: 3512
                         Len:
                                129
                                                    Weight:
                                                               1.00
Name: B US P896
                         Len:
                                129
                                      Check: 3297
                                                    Weight:
                                                               1.00
Name: B US RF M1
                                      Check: 5527
                         Len:
                                129
                                                    Weight:
                                                               1.00
Name: B_US_SF2 K
                         Len:
                                129
                                      Check: 3616
                                                    Weight:
                                                               1.00
Name: B_US_WEAU1
                         Len:
                                129
                                      Check: 4435
                                                    Weight:
                                                               1.00
Name: B_US_WR27_
                         Len:
                                129
                                      Check: 812
                                                  Weight:
                                                              1.00
Name: B_US_YU2_M
                         Len:
                                129
                                      Check: 4948
                                                   Weight:
                                                               1.00
Name: BF1 BR 93B
                         Len:
                                129
                                      Check: 3645
                                                    Weight:
                                                               1.00
Name: C_BR_92BR0
                         Len:
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                                      Check: 4262
                                                   Weight:
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Name: C BW 96BW0
                        Len:
                                129
                                      Check: 4323
                                                    Weight:
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Name: C_BW_96BW1
                                     Check: 3054
                        Len:
                                129
                                                    Weight:
                                                              1.00
Name: C_BW 96BW1
                                     Check: 3900
                        Len:
                                129
                                                   Weight:
                                                              1.00
Name: C BW 96BW1
                        Len:
                                129
                                      Check: 4051
                                                    Weight:
                                                              1.00
Name: C ET ETH22
                        Len:
                                129
                                      Check: 3843
                                                   Weight:
                                                              1.00
Name: C_IN_93IN1
                        Len:
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                                     Check: 2878
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                                                              1.00
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                                     Check: 4499
                                                   Weight:
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Name: C_IN_93IN9
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                        Len:
                                129
                                                   Weight:
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Name: C_IN_94IN1
                        Len:
                                     Check: 4362
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                                                   Weight:
                                                              1.00
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                        Len:
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                                     Check: 3765
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                        Len:
                                     Check: 4444
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                                                   Weight:
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Name: CRF01_AE_C
                        Len:
                                129
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                                                  Weight:
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 Name: CRF01_AE_T
                        Len:
                                129
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                                                  Weight:
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 Name: CRF01_AE T
                        Len:
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                                                  Weight:
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 Name: CRF01 AE T
                        Len:
                                129
                                     Check: 5202
                                                  Weight:
                                                            1.00
 Name: CRF02_AG_F
                                     Check: 5063
                        Len:
                                129
                                                 Weight:
                                                            1.00
 Name: CRF02 AG F
                        Len:
                                129
                                     Check: 3731
                                                  Weight:
                                                            1.00
 Name: CRF02 AG G
                        Len:
                               129
                                     Check: 2202
                                                  Weight:
                                                            1.00
 Name: CRF02 AG N
                        Len:
                               129
                                     Check: 4873
                                                  Weight:
                                                            1.00
 Name: CRF02 AG S
                        Len:
                                     Check: 3995
                               129
                                                 Weight:
                                                            1.00
 Name: CRF02_AG_S
                        Len:
                               129
                                     Check: 6502
                                                 Weight:
                                                            1.00
 Name: CRF03 AB R
                        Len:
                                129
                                     Check: 2858
                                                 Weight:
                                                            1.00
 Name: CRF03 AB R
                        Len:
                                     Check: 2808 Weight:
                               129
                                                            1.00
 Name: CRF04_cpx_
                        Len:
                               129
                                     Check: 3912 Weight:
                                                            1.00
 Name: CRF04_cpx_
                        Len:
                               129
                                     Check: 3700 Weight:
                                                            1.00
 Name: CRF04_cpx_
                        Len:
                               129
                                     Check: 3297 Weight:
                                                            1.00
 Name: CRF05 DF B
                        Len:
                                129
                                     Check: 3974 Weight:
                                                            1.00
 Name: CRF05 DF B
                        Len:
                                129
                                     Check: 4062
                                                 Weight:
                                                            1.00
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                        Len:
                               129
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                                                 Weight:
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                                                 Weight:
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                                                            1.00
 Name: D UG 94UG1
                        Len:
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                                    Check: 3298
                                                 Weight:
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 Name: F1 BE VI85
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 Name: F1 BR 93BR
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                                    Check: 3253
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                                                            1.00
 Name: F1_FR_MP41
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                               129 Check: 2465
                                                 Weight:
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 Name: F2_CM_MP25
                        Len:
                               129
                                    Check: 2231 Weight:
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 Name: F2KU BE VI
                               129 Check: 461 Weight:
                        Len:
                                                           1.00
 Name: G_BE_DRCBL
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                               129 Check: 3194 Weight:
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 Name: G NG 92NG0
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                               129 Check: 4325
                                                Weight:
                                                           1.00
 Name: G SE SE616
                        Len:
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                                    Check: 2614
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 Name: H BE VI991
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                                                           1.00
 Name: H_BE VI997
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                                                 Weight:
                                                           1.00
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                        Len:
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                                                 Weight:
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 Name: J SE SE788
                        Len:
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                                                 Weight:
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 Name: O CM ANT70
                        Len:
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                        Len:
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                        Len:
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                                                 Weight:
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00BW0762_1 MAGRSGD... NDDTLLQAVR IIKILYQSNP YPK.PEGTRQ ARRNRRRRWR
00BW0768_2 MAGRSEDS...DATLLQAVR IIKILYQSNP YPK.PEGTRQ ARKNRRRRRR
00BW0874_2
           MAGRSGD... SDEALLQAVR IIKVLYOSNP YPK.PEGTRQ ARKNRRRRWR
00BW1471_2
           MAGRSGD... SDEALLQAVR IIRILYQSNP YPKPEG.TRQ ARKNRRRRWR
00BW1616_2
           MAGRSGDS.. .DEALLQAVR TIKILYQSNP YPE.PKGTRQ ARKNRRRRWR
00BW1686 8
           MAGRSGDS....DEALLQAIK SIKILYQSNP YPE.PQGTRQ AQRNRRRRWR
00BW1759 3
           MAGRSGD... NDEAVLQAIR IIKILYQSNP YPK.PRGTRQ AQKNRRRRWR
00BW1773_2
           MAGRSGDS....DEALLQAVK IIKILYQSNP YPE.PKGTRQ ARKNRRRRWR
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00BW1783_5 MAGRSGD... SDEAVLQAVR IIKILYQSNP YPK.PEGTRQ ARKNRRRRWR
             MAGRSGD... GDAALLQAVR IIKILYQSNP YPK.PEGTRQ ARKNRRRRWR
 00BW1795_6
            MAGRSGD... SDEELLQVAR IIKILYQSNP YPE.PRGTRQ ARKNRRRRWR
 00BW1811 3
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A UG 92UG0
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AC_RW_92RW ARQRQIHSIS ERILSTCLGR PTEPVPFQLP PIERLTIDCS EDGGTSGTQQ
AC_SE_SE94 ARQRQIDSIS ERILSTCLGR SAEPVPLQLP PLERLHLD.....SGTQQ
ACD_SE_SE8 ARQRQIDSIS QRILSTCLGR SEEPVPLQLP PLERLNLDCC EDCGTSGTQG
ACG BE_VII ARQRHIHSLS ERILCTCLGR SEEPVHLPLP PLEGLTLDCN ESSGTSGTEG
AD_SE_SE69 ARQRQINSIG ERILSTYLGR SQEPVPLQLP PLERLTLNCI EDCGTSGTQG
AD_SE_SE71 ARQNQIDSIS KRILSNCLGR PAEPVPLQLP PLERLNLNCS KDCGTSGTQG
ADHK_NO_97 ARQXQIHSIG ERVLATCMGR PAEPVPLQLP PLERLTLDSS EDCDIAGKQG
ADK_CD_MAL ARQRQINSIG ERILSTYLGR PEEPVPLQLP PLERLTLNCN EDCGTSGTQG
AG_BE_VI11 ARQRHIQAIS RRILDACLGR PAEPVPLQLP PLERLSLDCS KDIGTSGTQR
AG NG 92NG
           ARQRQISALS ERILSTCLGR PAEPVPLQLP PIERLSLDCS EDSRTPETQQ
           ARQKQIHSIG ERVLATYLGR PAEPVPLQLP PLERLTLDCS EDCGTSGEKG
AGHU_GA VI
           ARQRQIHSLG ERILTTCLGR STEPVPFLLP PIERLRIDCS EDRGDSDPQG
AGU CD Z32
AJ_BW_BW21 ARQNQIDSIS ERILSTCLGR PTEPVPFQLP PIBRLRLDCS EDCGHSGTQG
B_AU_VH_AF ARQRQIRQIS GWILSTYLGR PAEPVPLQLP PLERLTLDCS KDCGTSGTQG
B_CN_RL42 ARQRQIREIS DRILVTYLGG STEPVPLQLP PLERLTLDCS KDCGTSGTQG
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QRQRQIQSIS ERILSTYLGR PEQPVPLPLP PLERLTLDCS EDCGTSGTQG
B DE D31 U
B_DE_HAN_U
            ERQROIRSIS ERILSTFLGR PARPVPLQLP PLERLTLDCS EDCGNSGTQG
            ERQRQIHSIS ERILGTYLGR SAEPVPLQLP PLERLTLDCN EDCGTSGTQG
B FR HXB2
            ERQRQIRKIS GWILSTYLGR SAEPVPLQLP PLERLNLDCS EDCGTSGTQG
B GA OYI M
            ERQRHIRAIS NWILSTHLGR PAEPVPLQLP PLERLTLDCS KDCGTSGTQG
B GB CAM1
B GB GB8 A
           ARQRQIHQIG EWILSAFLGR PAEPVPLQLP PIERLTLDCD EDCGTSGTQG
            GRQRQIQSLS AWILSTRLGR STQPVPLQLP PLERLTLDCS EDCGTSGTQG
B GB MANC
B_KR_WK_AF RRQWWIQSLS GWILNTHLGR PAEPVPLQLP PLERLTLDCN EECGTSGTQG
B_NL_3202A ERQRQIRSIS ERILSTYLGR SAEPVPLQLP PLERLTLDCD EDCGTSGTQG
B_TW_TWCYS ERQRQIRTIS GWILSNYLGR PAEPVPLQLP PLERLTLDCD EDCGTSGTQG
B_US_BC_LO ERQRQIRSIS ERILSTFLGR SAEPVPLQLP PLERLNLGCN EDCGTSGTQG
           QRQRQIQSIS GWILSNHLGR PADAVPLQLP PLERLTLDCN EDCGTSGTQG
B_US_DH123
           ERQRQIRTIS ERILSTYLGR PAEPVPLQLP PLERLTLDCN EDCGTSGTQG
B_US_JRCSF
B_US_MNCG_
           ERQRHIRSIS AWILSNYLGR PAEPVPLQLP P.QRLTLDCS EDCGTSGTQG
B US_P896
            ERQRQIRSIS ERILGTFLGR FEEPVPLPLP PLEKLTLDCN EDCGTSGTQG
            ERQRQIRRCS EWILDTYLGR SVDPVQLQLP PLERLTLDSS EDCGTSGTQG
B US RF M1
B US SF2 K
            ERQRQIRSIS GWILSTYLGR SAEPVPLQLP PLERLTLDCS EDCGNSGAQG
            ERQRQIRKIS GWILNTYLGR PTEPVPLPLP PLDRLTLDCK EDCGTSGTQG
B US WEAU1
            RORQIQSLS AWIISTHLGR PAEPVPLQLP PLERLTLDCS EDCGTSGTQG
B US WR27
B_US_YU2_M
           ERQRQIRSIS GWLLSNYLGR PTEPVPFQLP PLERLTLDCN EDCGTSGTQG
           ARQRQIREIS ERILSSCLGR PEEPVPLQLP PLERLHINCS EDCGQGTEEG
BF1_BR 93B
            ARQRQIHSIS ERILSTCVGR PAEPVPFQLP PIERLNINCS ESGGTSGTQQ
C_BR_92BR0
            ARORQIHSIS ERILSTCLGR PTEPVPLQLP PIERLHIDCS ESSGASGTQQ
C BW 96BW0
            ARQKQINSIS ERILSTCLGR SAEPVPFLLP PIERLHISDS ESGGTSGTQQ
C_BW_96BW1
C_BW 96BW1
            ARQRQIHSIS ERILSTCLGR PAEPVPLQLP PIERLHIGGS ENSGTTGTQQ
            ARQRQIDSIS TRILSTCLGR PEEPVPFQLP PIERLNIGDS ESGGTSGTQQ
C BW 96BW1
C ET ETH22 ARQRQIHTLS ERILSNFLGR PAEPVPLQLP PLERLNLDCS EDSGTSGTQQ
C IN 93IN1 ARQRQIHSIS ERILSTCLGR STEPVPLQLP PIERLHIGGS ESGGTSGTQQ
C_IN_93IN9 ARQRQIHSLS ERILSACLGR PAEPVPLQLP PLERLHISGS ESGGTSGTQQ
C_IN_93IN9 ARQKQIHSLS ERILSTCLGR SAEPVPLOLP PLERLHISGS ESGGTSGTQQ
C_IN_94IN1 ARQRQIHSIS ERILSACLGR PAEPVPLQLP PIERLHISGS ESGGTSGTQQ
C_IN_95IN2 ARQRQIHSIS ERILSTFLGR PAEPVPLQLP PIERLHISGS ESAGTSGTPQ
           RRQRQIHSLS ERILVACVGR STEPVPLQLP PLERLHIDCS EDCGTSGTQQ
CRF01_AE_C
CRF01 AE C
           ARQRQIHKIG ERILSTCLGR SPEPVPLQLP PLERLHLDCS EDCGTSGTQQ
           ARQRQIRALS ERILSACLGR SAEPVPLQLP PLERLHLDCS EDCGTSGTQQ
CRF01 AE C
CRF01_AE_T
           ARORQIRAIS ERILITCLGR STEPVPLQLP PLERLHLDCN EDCGTSGTQQ
CRF01_AE_T
           ARQRQIRAIS ERILNACVGR STEPVPLQLP PLERLHLDCS EDCGTSGTQQ
           ARQRQIRAIS ERILSTCLGR STEPVPLQLP PLERLHLDCS EDCGTSGTQQ
CRF01 AE T
           ARQRQIREIS ERILSSCVGR STEPVPLPLP PLERLHLDCS EDCGTSGTQQ
CRF01 AE T
           ARQRQISAIS ERILSTCLGR STEPVPLQLP PVERLNLDCS EDGGTSGTQQ
CRF01 AE T
           ARQRQISAIS ERILSACLGR STEPVSLPLP PLERLHLDCS EDCGTSGTQQ
CRF01 AE T
           ARQRQIRAIS ERFLSTCLGR SAEPVPLQLP PIERLCLDCS EGCGTSGTQQ
CRF02_AG_F
           ARQRQIRAIS QRILSTCLGR SAEPVPLQLP PLERLCLDCS EGCGTSGTQQ
CRF02_AG_F
           ARQRQIHSLS ERILSTCLGR PEEPVSFQLP PLERLNLDCS EDCGNSGTQS
CRF02_AG_G
           ARQRQIRAIS ERILSTCLGR SAEPVPLQLP PIERLNLDCS EDCGTSGTQL
CRF02_AG N
CRF02_AG_S ARQRQIRAIS ERILSTCLGR SAEPVPLQLP PIERLRLDCS EDCGTSGTQG
CRF02_AG_S ARQRQVRAIS ERILSTCLGR PAEPVPLPLP PIERLCLDCS EDSGTSGTQQ
CRF03_AB_R ERQRHIHSIS EQILSTYLGR PEEPVLLHLP PLERLTLDCS EDCGTSGTQG
CRF03_AB_R ERQRHIHSIS QRILSTYLGR PEEPVPLHLP PLERLTLDCS EDCGTSGTQG
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           ARQKQIHSLS ERILATYLGR PAEPVPLQLP PLEKLTLNCS EDCGTSGDKG
CRF04_cpx_
           ARQKQIHSIS ERVLATYLGR PAEPVPLQLP PLEKLTLNCS EDCGTSGEKG
           ARQNRIHSIS ERILAACLGR PAEPVPLQLP PIEKLTLDCS EDCGTSGDKG
CRF04_cpx_
CRF05 DF B
           ARQRQINSIG ERLLSTYLGR SEEPVPLQLP PLERLNLNCS EDCGTSGTQG
CRF05_DF_B ARQRQIRSIA DRIVDTYLGR PEEPVPLQLP PLERLNLNCS EDCGTSGTQG
CRF06_cpx_
           ARQNQIDSIS ERVLSTCLGR SAEPVPLQLP PIERLRLDCS EDCGNSGTQG
CRF06_cpx_
           ARQNQIDSIS ERILSTCLGR PTEPVPFQLP PIERLRLDCS EDCGNSGTQG
CRF06_cpx_
           ARQKQIDSIS ERILSTCLGR SAEPVPLQLP PIERLRLDCS EDCGNSGTQG
CRF06_cpx_
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CRF11_cpx_
           ARQNQIDSIS QRILSDCLGR SEEPVPLQLP PIERLHLDCS EDCGNPGTQG
CRF11_cpx
           ARQNQLHSIS QRILSTCLGR SEEPVPLPLP PIERLHLDCS EDCGNSGTQG
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D_CD_ELI_K
D_CD_NDK_M
          ARQRQIHSIG ERIICTFLGR PEEPVPLQLP PLERLNLNCS EDCGTSGTQG
D UG 94UG1
          ARQRQIHSIG ERIISTYLGR FEEPVPLQLP PLERLNLNCS EDCGTSGTQG
          ARQRQIRALS DRILSSCLGR SEEPVPLQLP PLERLHINCS EDCGQGPEEG
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F1 BR 93BR
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F1_FI_FIN9
F1 FR MP41
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F2 CM MP25
          ARQRQIHQIS ERILSTCLGR LQEPVRLQLP LLEKLHINCS EDCGQGTEKG
F2KU BE VI
          ARQRQIHSIS QRILSTCLGR PAEPVPFQLP PLERLNLDCS EDSREGAEGE
G_BE_DRCBL
          ARQRQIHSIS ERILSTCLGR PEEPVPLQLP PLERLHLDCS EDGGTSGTQQ
G_NG_92NG0
          ARQRQIHSIS ERILSACLGR PAEPVPFQLP PLEGLSLDCS KDGGTSGTQQ
G_SE SE616
          ARQRQISAIS ERILTAYLGR PAEPVPLQLP PLERLHLDCS EDSGTSGTQQ
H_BE_VI991
          ARQRQIHSIG ERVLATCLGG PAEPVPLQLP PLERLTLDCS EDCGTSGEKG
H_BE_VI997
          ARQRQIRAIS ERILTDCLGR PPEPVPLQLP PLERLTLDCN KDCGTSGEKG
H_CF_90CF0
          ARQRQIREIS ERILTSCLGR PPEPVTLQLP PLERLTLNCS EDCGTSGEKG
J SE SE702
          ARQNQIDSIS ERILSSCLGR PAEPVPLQLP PIERLRLDCS EDCGNSGTQG
          ARQNQIDSIS ERIPSSCLGR PAEPVPLQLP PIERLRLDCS EDCGNSGTQG
J SE SE788
K CD EOTB1
          ARORQIREIS QRVLSSCLGR STEPVPLQLP PLERLSLNCD EDSGQGTEGE
K_CM_MP535
          ARQKQISSIS ERLLSACLGR SAEPVPLQLP PIEKLNLNCD EDPGKGTEGG
          ARQRQIRAIS ERILSSCLGG PPEPVDLPLP PLDRLTLDTE EDSGTPGTES
N CM YBF30
O_CM_ANT70
          RRQAQVDTLA ARVLATVVHG PQNNNIVDLP PLEQLSIRDP EGDQLSEAWT
O CM MVP51
          RRQAQVDSLA TRILATVVHG SQDNNLVDLP PLEQLNIRDP EADRLPGTGT
O_SN_MP129
          TRHAHVDTLA ARILATVVHG PQDNNLVELP PLEQLSIRDP DGDQPSGTWT
          KRQAQIDTLA ARILATVVHG PQDNNLVELP PLEQLSIRDP DGDQPSGTWT
O SN MP130
          RRQQQIRSIS ERILSTCLGR PAEPVHLQLP PLERLNLDCS ....KGTATG
U_CD___83C
          101
                                  129
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          SQGTSEGVGS P.....
00BW0768 2
00BW0874_2
          SQGTTEGVGN P......
00BW1471_2
         SQGITEGVGS P......
00BW1616_2
          ....TQGVGS P.....
         SQGATEGVGN P......
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00BW1759_3
          .....VGS P.......
00BW1773_2
          SQGTTEGVGS P.....
00BW1783 5
          SQGTTEGVGN P.....
00BW1795 6
         SQGTPEGVGN P......
         SQGTPEGVGN P......
00BW1811 3
         SQGTTEGVGS P.....
00BW1859 5
00BW1880_2 SQGTPEGVGN P......
00BW1921_1 SQGTTEGVGN P......
00BW2036_1
         SQGTTEGVGS P.....
00BW2063_6
          SQGTPEGVGN P.....
          PQGTTEGVGN P.....
00BW2087_2
00BW2127 2
          .....VGS P.......
00BW2276 7
          SQGTTEGVGS P.....
00BW3819_3
          SQGTTEGVGS P.....
00BW3842 8
         PQGTTEGVGS P......
00BW3871 3
         SQGTTEGVGN P......
00BW3876_9 SQGTKEGVGS P.......
00BW3886_8 SQGTTEGVGS P........
00BW3891_6 SQGTTEGVGS P.......
00BW3970_2
         .....GVGH P......
00BW5031_1
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96BW01B21
         SQGTTEGVGN P.....
         SQGTTEGVGN P.....
 96BW0407
 96BW0502
          ....TEGVGS P.....
         SQGPTEGVGS P......
96BW06 J4
96BW11 06
         SQGTPEGVGN P.....
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96BW1210 SQGTTEGVGS P......
 96BW15B03 SQGTTEGVGS P.......
           .....GVGS P.....
 96BW16_26
 96BW17A09 SQGATEGVGS P.....
 96BWMO1_5
           SQGTPEGVGN P......
           SQGTTEGVGS S.....
 96BWM03_2
98BWMC12 2
           SQGTAEGVGS P.....
           SHGTPEGVGN P.....
98BWMC13_4
           ....TQGVGN P.....
98BWMC14 a
98BWMO14_1 SLGTTEGVGS P.......
98BWM018_d SQGTTEGVGN P.......
98BWMO36_a PQGTTEGVGN P.......
98BWMO37_d PQGTTEGVGS P.....
99BW3932_1 SQGTTEGVGS P.......
99BW4642_4 SQGTTEGVGS P.......
           SQGTTEGVGS P.......
99BW4745_8
99BW4754_7
           SQGTPEGVGN S.....
           SQGTTEGVGS P.....
99BWMC16 8
A2 CD 97CD
           SQGAETGVGR PQTSVESSGI LGSGIEDX.
A2_CY_94CY
          SQGTETGVGR SQESVESSVI LGSGTEEX.
A2D 97KR
          PQGTETGVGR PQISVEPSVV LGSGTEEX.
           PQGTETGVGG .TIFVESSVI LGSRTKEQX
A2G CD 97C
A BY 97BL0
          SOXTETXVXX PQISXESSXI XXSGTKEX.
A_KE_Q23_A
          SQGAETGVGR HQVSVESPVI LGSGTKNX.
A_SE_SE659
           SQGVETGVGR PQVSGESPVI LGSGTKNX.
A_SE_SE725
           SQGVETGVGR PQVPGEPSTV LGSGTKTX.
A_SE_SE753
           SQGIETGVGR PQVSVESPVI LGSGTKEX.
A_SE SE853
           .....VGR PQVSVESPGV LDSGTKNX.
A SE SE889
           SQGAETGVGG PQVSEESSII LGSGTKTX.
A SE UGSE8
          ····· TQVSGESSVV LDSGTKDX.
          SQGVETGVGR TQVSGESPVV LGSGTKNX.
A UC 92UG0
A_UG_U455
           PQGTETGVGG PQISVESSAV LGSGTKNX.
AC_IN_2130
          SQGVETGVGR PQVSVESPGI LGSGTKNX.
AC_RW_92RW SOGTTEGVGN PVSRKSCAVL GSGTKKEX.
AC_SE_SE94
          SQGTETGVGR PQVSVESSAI LGPGTKNX.
ACD_SE_SE8
          .....VGS NQISVESPAV LDSGTKEX.
ACG BE VI1
          .....VGS SQTSGEHPVI LESGTKEX.
          .....VGS PQIPVEPPAV LDSGTKEX.
AD_SE_SE69
AD SE SE71
          .....VGS PQIPVESPAI LDSGTENX.
ADHK NO 97
          .....VGD PQIPGESSAV LGTGTKEX.
ADK CD MAL
          .....VGS PQISVESPAI LGSGTEEX.
          SQGTETGVGR PQIFVESSGV LGSGTKEX.
AG BE VI11
          SPGTETGVGG PQISVESPVV LGSGTKEX.
AG NG 92NG
AGHU_GA_VI
          ......VGS PQISVESPTV LGTGAKEX.
AGU_CD_Z32
          .....VGD SQIPGESCDL LGSGTKEX.
AJ BW BW21
          .....VGD PQVSGESCPI LGEGTKEX.
B AU VH AF
          .....VGG PQVLVESPAV LESGAAEX.
B CN RL42
          .....VGS PQILVESPAV LDSGTKEX.
B_DE_D31 U
          .....VGS PQILVESPAV LESGTKEX.
B_DE_HAN_U
          .....VGS PQVLVESPAV LEPGTKEX.
B FR HXB2
          .....VGS PQILVESPTV LESGTKEX.
B GA OYI M
          ......VGS PEILVESPAV LEPGTKEX.
B GB CAM1
          .....VCS PQILVESPAV LESGTKEX.
          ......VGS PQVLVESPAV LDPGTKEX.
B GB GB8 A
B GB MANC
          ......VGN PQVLVESPAV LESGSKEX.
B_KR_WK_AF
          .....VGN PQILVESPAV LESGTKEX.
B_NL_3202A
          ......VGS PQILVESPAV LESGTKEX.
B_TW_TWCYS
          ......VGS PQIFVESPTV LDSGTKEX.
B_US_BC LO
          .....VGS PQVLVESPTV LEPGTKEX.
B US DH123
          .....VGT PQILVESPAV LESGTKEX.
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.....VGN PEILVESPTV LESGTKEX.
B US JRCSF
B_US_MINCG_
           ......VGS PQILVESPTV LESGTKEX.
B_US_P896_
            .....VGS PQILVESPAI LEPGTKEX.
B_US_RF_M1
           .....VGS PQVLVESPAV LESGAKEX.
           ......VGS PQILVESPAV LDSGTKEX.
B US SF2 K
B US WEAU1
           .....VGS SQILLESPAV LEPGTKEX.
B_US_WR27
            .....VGD PQILGESPTV LGSGAKEX.
B US YU2 M
           .....VGS PQILVESPPV LDSGTKEX.
BF1 BR 93B
           .....VGS PQTSGESRAV LESGTKEX.
           POGNTERVGN PVFGRPCAVL ESRVKKEX.
C BR 92BR0
C_BW_96BW0 SQGTTEGVGN PVSGKSCAIL GSRAKKEX.
C_BW_96BW1 SQGTPEGVGN PISGKSCAVL GARAKKEX.
C_BW_96BW1 SQGTTEGVGS PISGKSCAVL GSGTKKEX.
C_BW_96BW1
           SQGTTEGVGS PVSGKSCAVL GSGTKKEX.
           SQGTTEGVGN PISGKPCAVL GSGAKKEX.
C ET ETH22
C IN 931N1
           ....L..GS PISGKSCAVL GSGAKKEX.
C_IN 93IN9
           SQGTTERVGS PISGKSCAVL GSGAKKEX.
C IN 931N9
           SQGTTEGVGS PISGKSCAVL GYRAKKEX.
C IN 94IN1
           SQGTTERVGS PISGKSCAVL GSGAKKEX.
           SQGTTEGVGS PISGKSCTVL GSGABKEX.
C IN 951N2
CRF01_AE_C SQGTETGVGG PQISGESSVI LGSGTKNX.
CRF01_AE_C STGTETEVGR PQISGESSVI LGSGTKNX.
CRF01_AE_C
           SRGTETGVGR PQISGESSVI LGSGTENX.
CRF01_AE_T
           SQGTETGVGR PQISGESSVI LGPGTKNX.
CRF01_AE_T
           SQGTETGVGR PQISGESSVI LGSGTKNX.
CRF01 AE T
           SQGTETGVGR PQISGESSVI LGPGTKNX.
CRF01_AE_T
           SQGTETGVGR PQISGESPVI LGPGTKNX.
CRF01 AE T SQGTETGVGR PQISGESSVI LGPGTKNX.
CRF01 AE_T SQGTETGVGR PQISVESSGI LGPGTKNX.
CRF02_AG_F POGTETGVGS PPISGESSTI LGSGTKEX.
CRF02_AG_F SQGTETGLGS PQISGESSDI LGAGTKEX.
CRF02_AG_G
           ......VAD PQIPGESRAI LGSGTKEX.
CRF02_AG_N SQGTETGVGS PQISVESYII LGSGTKEX.
CRF02 AG S
           .....VGS PQISVESSIV LGSGTKEX.
CRF02 AG S
           SQGTETGVGS SQTSVESSVI LGSGTKEX.
CRF03_AB_R
           .....VGS PQILVESPTV LDSGTKEX.
CRF03_AB_R
           .....VGS PQILVESPTV LDSGTKEX.
CRF04_cpx_
           .....VGS PQVSVELPAV LGTCAKEX.
CRF04_cpx_
           .....VGS PQVSVEPPAV LGTGAKEX.
CRF04_cpx_
           .....VGN PQVPVEPPAV LGTGDKEX.
CRF05 DF B
           ......VGS PQISVEPPAI LESGTKEX.
CRF05 DF B
           .....VGS PQISVESPTV LESGAKEX.
CRF06_cpx_
           .....VGN PQISGEPDML LGTGTTEX.
CRF06_cpx_
           .....VGD PQIPGEPGVV LGTGTKEX.
CRF06_cpx_
           .....VGD PQIPVEPGVL LGTGTKEX.
CRF06_cpx_
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CRF11_cpx_
           .....VGD SQISGESDTV LGPRTEEX.
CRF11_cpx
           .....VGE SQIPGESSTV LGPRTEEX.
D CD 84ZRO
           .....VGS PQISVESPAI LESRTEEX.
D CD ELI_K ......VGH PQISVESPTV LESGTEEQX
D_CD_NDK_M .....VGS PQIPVEPPAV LESGTEEX.
D_UG_94UG1 .....VGS HQISVESPAV LDSGTKEX.
F1_BE_VI85 ......VGS SQISGESHAV LESGTKEX.
F1_BR_93BR ......VGS SQISGESHTV LGSGTKEX.
F1_FI_FIN9 ......VGS PQISGEHHTV LESGTKEX.
F1_FR_MP41 .....VGN PQISMEPRTV LESGTKEX.
F2_CM_MP25 .....VGS PQISVESRAV LGSGTKEX.
F2KU_BE VI
           .....LGN PQIPVEPCAV LGSGTKEX.
G_BB_DRCBL SQGTEIGVGS PQIFVBSSVV LGSGTKEX.
G_NG_92NG0 PQGTETGVGR PQVLVEPPVV LGSGTKEX.
```

68458026 032883

G_SE_SE616	POGTETGVGR	.SIFVESSVV	LGQGTKEX.
H_BE_VI991	VGS	PQTSGESPAV	LGTGAKEX.
H_BE_VI997	KGG	PQIPVESSTV	LGTGTKEX.
H_CF_90CF0	EGS	PQISLESSTI	LGTGTKEX.
J_SE_SE702	VGD	PQISGEPCMV	LGAGTKEX.
J_SE_SE788		PQISGEPCMV	
K_CD_EQTB1	LGS	PQIPVEPDTV	LGSGDKEX.
K_CM_MP535	LGS	PQISVEPCTV	LESGTKEX.
N_CM_YBF30	QQG.TATTET	QNTLVGNTCI	LGKRVKGX.
O_CM_ANT70	VDPR.AEDNC	LQNLCSCNTI	LATRIAEX.
O_CM_MVP51	VDPG.TKDNS	LT.LWSCNAI	LATRIEKX.
O_SN_MP129	VDSG.TEDNC	LQTLHSCNTI	LATRVAEX.
O_SN_MP130	VDPG.TEDNC	LQNLHSCNTI	LATRVAEX.
U CD 83C	VGS	TOTPGESCAV	LCCCTKE

Table 16. HIV Tat Alignment GCG Multiple Sequence File. Written by Omiga 1.1

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                                      Check: 4583
                                                     Weight:
                                                                1.00
Name: 00BW0874
                         Len:
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                                      Check: 5462
                                                     Weight:
                                                                1.00
Name: 00BW1471
                         Len:
                                 108
                                      Check: 4359
                                                     Weight:
                                                                1.00
Name: 00BW1616 2
                                      Check: 5389
                         Len:
                                 108
                                                     Weight:
                                                                1.00
Name: 00BW1686 8
                         Len:
                                 108
                                      Check: 6742
                                                     Weight:
                                                                1.00
Name: 00BW1759 3
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AD_SE_95_S GRKKRKQRR. .GAPPSSKDH QNPIPKQPIP QTQG.ISTGP KESKKEVESK
ADHK_NO_97 GRKKRRPRR. .RPPKSSQDH QDFIPKQPLS .RTHGEPTGP KEKKK.VASK
ADK_CD_85_ GRKKRRQRR. .RPPQGNQAH QDPLPEQPSS QHRGDHPTGP KEKKK.VESK
AG_BE__VI GRKNRKHRR. .GTPQGSKDH QNPVPKQSLP LIRG.IPTGP EESKKEVASK
AG_NG_92_9
            GRKKRRRRR. GTPQSHQDH QNPVPKQPLP TTRG.NPTGP KESKKEVESK
            GRKKRSQRR. .RAPKSSPDH QNLVPKQPFS .RTNGNPTGP KEKKK.VASK
AGHU GA
             GRKKRRORR. .GTPQDRKDH QNPVPRQPLP TTRG.NPTGP KESKKEVESK
AGU CD 76
AJ_BW_98_B GRKKRRQRR. .TAPPGNKNH QDLVQEQPLS .QTQRKSTGP EESKKEVESK
B_AU__VH
            GRKKRRORR. .RAPEDSOTH QVSLSKQSAP QPRGD.PTGP KESKKKVESK
GRKKRRORR. .RAPQDSOTH QASLSKQPAS QPRGD.PAGP KESKKKVESE
B CN RL4
```

```
GRKKRRQRR. .RAPEDSQTH QVSLSKQPAS QPRGD.PTGP KESKKKVETE
 B_DE_86_D3
             GRKKRRORR. .RAPODSOTH QVSLPKOPSS QORGD.PDSP KKSKKKVERE
 B DE 86 HA
             GRKKRRORR. .RAHQNSQTH QASLSKOPTS QPRGD.PTGP KE.KKKVERE
B_FR_83_HX
             GRKKRRORR. . RAPODSKTH QVSLSKOPAS QPRGD . PTGP KESKKKVERE
B GA
        OYI
             GRKKRRQRR. .RTPQSSKTH QASLSKQPAS QFQGD.PTGP KESKKKVEGE
B GB
        CAM
             GRKKRRORR. .RLPEDSQIH QVSLPKOPTS QPQGD.PTGP KESKKKVESK
B GB
        GB8
             GRKKRRORR. RAPPDSOTR OVSLSKOPTS OPRGD.PTGP EESKKKVERE
B GB 59 MA
             GRKKRRORR. .RAPODNKNH QVSLSKOPTS RARGD.PTGQ EESKEKVEKE
B KR
        WK
             GRKKRRORR. RSPODSETH QVSLSKOPAS QPRGD.PTGP KESKKKVERE
B_NL 86 32
             GRKKRRORR. . RTPONSOTH QADLSKOPTS QPRGD.QTGQ KESTKKVERE
B TW
        TWC
             GRKKRRKRR. .RSPQHSQTD QASLSKQPAS QPRGD.PTGP KESKKKVETE
B US
        DH1
             GRKKRRQRR. .RPPQDSQTH QVSLSKQPSS QPRGD.PTGP KEQKKKVERE
B_US
        P89
             GRKKRRQRR. .GPPQGSQTH QVSLSKQPTS QPRGD.PTGP KESKEKVERE
B_US_83 RF
B_US_83_SF
             GRKKRRORR. . RAPODSOTH QASLSKOPAS QSRGD.PTGP TESKKKVERE
B US 84 MN
             GRKKRRORR. .RAPEDSQTH QVSLPKQPAP QFRGD.PTGP KESKKKVERE
             GRKKRRQRR. . RPPQDSQTH QVSLPKQPSS QQRGD.PTGP KESKKKVERE
B US 86 JR
             GRKKRRORR. . RPPODSOTH OSSLSKOPTS QLRGD. PTGP TESKKKVERE
B_US 86 YU
             GRKKRRORR. . RAPODSOTH QASLSKOPTS QPRGD. PTGP KESKKKVERE
B_US_87_BC
             GRKKRRORR. .RAPPEGLTH QVPLSKQPSS QFRGD.PTGP KESKKKVVRE
B_US_88_WR
             GRKKRRQRR. .RSPQNSQTH QDSLSKQPTS QPRGD.PTGP KESKKKVERE
B_US_90_WE
BF1 BR_93_
             GRKKRRQRH. .RTPQSSQLH QDPVPKQPAS QAQGN.PTGP KESKKEVESQ
             GRKKRRORR. .SAPPSSEDH QNPIPKQPLP .QTRGDQTGS EESKKKVESK
C_BR_92_92
             GRKKRRORR. SAPPSSEDH ONPVSKOPLP OTRGDPTGL EESKKKVESK
GRKKRRORR. SAPPSSKDH ONPVSKOPLP OTRGDPTGS KESKKKVESK
C_BW 96 96
C_BW_96 96
C_BW_96_96
             GRKKRRQRR. .SAPPSSEDH QDLVPKQPLS .QARGNPTSS KESKKKVESK
            GRKKRGORR. .SAPPRSEDH ONLISKOPLP .RTOGDSTGS EESKKKVESK
C BW 96 96
            GRKKRRORR. . RAPOSSKOH ONLISKOPLS .HTRGDPTGS EESKKKVESK
C ET 86 ET
            GRKKRRORR. .SAPPSSEDH ONLISKOPLP .RTOGDPTGS EESKKKVESK
C IN 93 93
            GRKKRRORR. RAPOSSEDH ONLISKOPLP RTOGDPTGS EESKKKVESK
C_IN_93 93
            GRKKRRQRR. .SAPPSSEDH QNLISKQPLP .RTQGDPTGS EESKKKVESK
GRKKRRQRR. .SAPQSSEDH QDLISKQPLP .RTQGDPTGS EESKKKVEGK
C_IN_93_93
C_IN_94_94
            GRKKRRORR. .SAPOSSEDH ONPISKOPLP .RTPGDPTGS EESKKKVESK
C_IN_95_95
            GRKKRKHRR. .GPPPGSKDH QNPIPKQPLP TTRG.NPTGP KESKKEVAKK
CRF01 AE C
            GRKKRKHRR. .GPSQDSKDH QNSIPKQPLP TSRG.NPTGP KESKKKVESK
CRF01 AE C
CRF01 AE C
            GRKKRKHRR. .GTPQGSKGH QDPISKQPLP IIRG.NPTGP KESKKEVESK
CRF01_AE_T
            GRKKRKHRR. .GTPQSSKDH QNPIPKQPLP IIRR.NPTDP KESKKEVASK
            GRKKRKHRR. .GTPQSRKDH QHPIPEQPLS IIRG.NPTDP KESKKEVASK
CRF01 AE T
            GRKKRKHRR. .GTPQSSKDH QSPIPEQPLP IIRG.NPTDP KESKKEVASK
CRF01 AE T
            GRKKRKHRR. .GTPQSRKDH QYPIPEQPLP IIRGGNPTDP KESKKEVASK
CRF01 AE T
            GRKKRKHRR. .GTPQSSKDH QTPIRKQPPS IIRG.NPTDP KESKKKVESK
CRF01_AE_T
            GRKKRKHRR. .RTPQSSKDH QYPIPEQPSP IIRG.IPTDP KESKKEVASK
CRF01_AE_T
            GRKKRRRRR. .GTPQSRQDH QNPVPKQPLP TTRG.DPTDP KESKKEVASK
CRF02_AG_F
CRF02_AG_F
            GRKKRXRRR. .GTPQSRQDR QNPVSKQPLP TTRG.NPTGP KESKREVESK
            GRKKRRRRR. .GTPQSHQDH QNPVSKQSLP QTRG.DPTGP KESKKEVESK
CRF02_AG_G
CRF02 AG N
            GRKKRRRRR. .GTPQSRQDH QNPVPKQPLP TTRG.NPTDP KESKKEVESK
            GRKKRKRRR. .GTPQSRQDN QDPVPKQPLP TTRG.NPAGP KESKKEVAGK
CRF02 AG S
CRF02 AG S
            GRKKRRRRR. .GTPQSRQDH QNPVPKQPLP TTRG.EQTGP KESKKEVASK
            GRKKRRORR. . RAPODNOTD QVSLPKOPAS QPRGD. PTGP KE.KKKMERE
CRF03 AB R
            GRKKRRORR. .RPPQDNQTD QVSLPKQPAS QPRGD.PTGP KE.KKKVERE
CRF03 AB R
CRF04_cpx_
            GRKKRKHRR. .GSLQGSKGH QNLIPKQPLS QQPNGDSTGP EEQKKKVASK
            GRKKRKRNE. .DLLGFSRDR QNPIPKQPLS Q.PNGNPEGP KEQKKKVASK
CRF04_cpx_
            GRKKRKHRR. .RPPQGSRDR QNPIPKQPLS QQHSGDPTGP KEQKEAVASK
CRF04_cpx_
            GRKKRRPRR. .RPPQGSQAH QDPVPEQPPS QPRGD.PTGP KKQKKEVESK
CRF05_DF_B
            GRKKRRSRR. .RPPQGGQAH QIPVPEQPSS QARGD.PTGQ KEQKKKVESK
CRF05 DF B
            GRKKRRORR. . QAPPGSKNH QDPVSKQPLS . . QTQREQTGP EKSKKEVESK
CRF06_cpx_
CRF06_cpx_
            GRKKRRORR. . TAPPGSKNH QDPVPKQPLS . QTQRGPTGP EKSKKKVESK
CRF06_cpx_
            GRKKRRORR. .TAPPGSKNH QDPVPKQPLS .QTQRKSTGP EESKKEVESK
CRF06_cpx_
            GRKKRRORR. .TAPLGSKSH QDPVPKQPLS .QTQRESTGP EKSKEEVESK GRKKRRORR. .AASHSSENH QDPIPKQPST .QPNRKPTGP EESKKEVESK
CRF11_cpx_
            GRKKWRQRR. .TASRSSKNH QDPIPEQPLP .QASRNPTGP EEPKKEVESK
CRF11_cpx_
```

```
D_CD_83_EL GRKKRRQRR. .GPPQGGQAH QVPIPKQPSS QPRGD.PTGP KEQKKKVESE
D_CD_83_ND GRKKRRQRR. .KPPQGDQAH QVPIPEQPSS QSRGD.PTGP K.KKKKVESE
D_CD_84_84 GRKKRRQRR. .RPPHSSQTH QDPIPKQPSS QPRGD.PTGQ KEKKK.VESK
D_UG_94_94 GRKKRRPRR. .RTPPGGQAN QDPVPKQPSS QPRGN.PTGP KEKKK.VESE
F1_BE_93_V GRKKRRQRH. .RTPQSSQVH QNSLPKQPLS QARGD.PTGP KESKKEVESK
F1_BR_93_9 GRKKRRQRP. .RTPQSSQIH QDFVPKQPIS QARGN.PTGP KESKKEVESK
             GRKKRRORH. .RTPQSSQIH QDPVPKQPLS QPRRN.PTGP KESKKEVESK
F1 FI 93 F
F1 FR 96 M
             GRKKRRQRR. .RTPQSSQSH KNPIPEQPLS QARGD.PTGP KESKKEVESK
F2_CM_95_M
             GRKKRRQRR. .RTPQSGEVH QDPVSKQPLS QTRGD.PKGP EESKKKVESK
F2KU BE 94
             GRKKRRQRR. .RTPQSSQAH QNPISKQPLS QARGD.PTGP KEPKKEVESK
            GRKKRKHRR. .GTPHSSKDH QTPVPKQPFS TTRG.NPTGP QESKKEVESK
G BE 96 DR
            GRKKRRPRR. .GTPQGSKDH QNPVPKQPLP ITSG.NPTGS EKPKKEVASK
G_NG 92 92
G_SE_93 SE
             GRKKRKHRR. .GTPQSSKGH QDPVPKQPLP TTRG.NPTGP KESKKEVASK
H_BE___VI9 GRKKRRQRR. .GTPKSLQDH QTLIPKQPLS .RTSGDPTGP EKKKK.VASK
H_BE___VI9 GRKKRSRRR. .ATPASVQDH QNHIPKOPLS .RTRGDPTGP KEKKK VASK
            GRKKRSRRR. .ATPASVQDH QNHIPKQPLS .RTRGDPTGP KEKKK.VASK
H_CF_90_90
             GRKKRSQRH. .RTPASLQDH QNSISKQPLS .RTHGDPTGP KEQKKEVASK
J_SE_93_SE
            GRKKRRQRR. .SAPPGSKTH QDLIPKQPLS .QTQRKPTGP EESKKEVESK
             GRKKRRQRR. .SAPPGSKNH QDLIPEQPLF .QTQRKPTGP EESKKEVESK
J_SE 94 SE
K CD 97 EQ
            GREKRRORT. .TTPYASKNH KDPIPKQPLP .QARGDPTGP KESKKEVESK
            GRKKRRPRR. .TTPYNSENH QDPLRKQPLS .QPRGEQTDP KESKKKVESK
GRKKRSQRR. .RTPQSSKSH QDLIPEQPLS .QQQGDQTGQ KKQKEALESK
K CM 96 MP
N_CM_95 YB
            GRKK...RGR PAAAS.HPDH KDPVPKQSPT ITK.RKQERQ EEQEEEVEKK
O CM ANT
O CM 91 MV
            GRKK...RRR PAAAASYPDN KDPVPEQSLS HTG.RKQKRQ EEQEKKVEKE
O_SN__99S GRKK...RRR PAAAARHPDN QDIVPEQLTY ITN.RKQKRQ EEQEKEVENE
O_SN___99S
            GRKK...RRR PAAAARNPDN QDIVPEQPPP ITNNRKHKRQ EEQEKEVEKE
       __83C GRKKRGKRR. .RTPQSGPNH QNIVSKQPSS QPRGD.PTGQ EEPKKKVEKK
U CD
             101 108
00BW0762 1
            TETDPFD.
00BW0768_2
            TKTDQFD.
00BW0874 2
            TKTDQFD.
00BW1471 2
            TEADPCD.
00BW1616 2
            TETDPFD.
00BW1686_8
            TKTDPFD.
00BW1759_3
            TETDRFD.
00BW1773_2
            TETDPD.
00BW1783_5
            TETDPFD.
00BW1795_6
            TETDPFD.
00BW1811 3
            TETDPD..
00BW1859_5
            TETDPYD.
00BW1880_2 TETNPFD.
00BW1921 1 TEADQFD.
00BW2036 1 TEADRED.
00BW2063_6 TETDPFD.
00BW2087_2 TERDPFD.
00BW2127_2 TTTDPFD.
00BW2276_7
            TETDPYD.
00BW3819_3
            TKTDPFD.
00BW3842 8
            TETDRFD.
00BW3871_3
            TKTDQFD.
00BW3876_9
            TKADPFD.
00BW3886_8
            AETDQFDY
00BW3891 6
            TETDPFA.
00BW3970 2
            TERDPFA.
00BW5031 1
            TETDPFDW
96BW01B21
            TKTDPFD.
 96BW0407
           TEADPFD.
 96BW0502
           TEADPFA.
96BW06 J4
            TETDOFD.
96BW11 06
           TETDOFD.
```

EG458026 T32803

```
96BW1210
              TETDPFD.
  96BW15B03
              TETDRFD.
  96BW16 26
              TETDPCD.
  96BW17Ã09
              TEADPFD.
  96BWMO1 5
              TKTDQFD.
  96BWMO3_2
              TETDPFD.
 98BWMC12_2
              TKAHPFD.
 98BWMC13_4
              TETDQFD.
 98BWMC14_a
              TDTDQFA.
 98BWM014_1
              TETDPCA.
 98BWM018_d
              TETDOFD.
 98BWM036_a
              TETDPFD.
 98BWM037_d
              TETDPFD.
 99BW3932_1
              TETDPFD.
 99BW4642 4
              TETDQFA.
 99BW4745_8
             TEPDPCD.
 99BW4754 7
             TETDPFD.
 99BWMC16_8
             TEADRFD.
 A2_CD___97
             AETDRFD.
 A2_CY___94
             AETDRFD.
 A2D 97 9
A2G CD 9
             AETDPCD.
             TETDPD..
 A_BY 97 97
             AETDOFD.
 A_KE_93_Q2
             AEADRFD.
 A_SE_93_SE
             AETDRFD.
 A_SE_94 SE
             AEADRFD.
 A SE 94 SE AETDRFD.
 A_SE 95 SE
             TEADRFD.
 A_SE_95 SE TETDRFA.
A_SE_95_UG AETDRFA.
A_UG_85_U4
A_UG_92_92
             AKTDRFA.
             TEADRYA.
AC_IN_95_2
AC_RW_92_9
             AKTORFD.
             TEADPFD.
AC_SE_96 S
             TETDRFD.
ACD_SE_95_
             AETDRFD.
ACG BE V
             TETHPLA.
AD SE 93 S
             ABADOFDW
AD_SE_95 S
             TEPDRFD.
ADHK NO 97
             TXTDPFDW
ADK_CD_85_
AG_BE__VI
AG_NG_92_9
             AEADQFDW
             TETHPGD.
             TETDOCA.
AGHU GA
             AEADPFDW
AGU CD 76
             TETDPFAW
AJ_BW_98_B AKPDRFD.
B AU VH
             TETNPSD.
B CN RL4
            TETDPRD.
B_DE_86 D3 TETDPID.
B_DE_86_HA TEADPFD.
B_FR_83_HX TETDPFD.
B_GA__OYI
B_GB__CAM
B_GB__GB8
            TETDPED.
            TETHPGD.
            TETDPSDW
B GB 59 MA
            TETDPVA.
B_KR WK
             TVVDPVT.
B_NL_86_32
            TETDPVD.
B TW TWC
            TETDPNDO
B US
       DH1
            TETDPVH.
B_US
     __P89
            TETDPVH.
```

```
B US 83 RF
             TETDPAVQ
B_US_83_SF
            TETDPFD.
B US 84 MN
            TETHPVD.
B US 86 JR
             TETOPON.
B_US_86_YU
            TETDPVH.
B_US_87_BC
            TETDPVD.
B_US_88_WR
            TETDPIA.
B_US_90 WE
            TETDPED.
BF1 BR 93
            AKTOPD...
C_BR_92_92
C_BW_96_96
            TETOPFD.
            TETDPFD.
C_BW_96_96
            TETDQFD.
C_BW_96_96
            TETDPFD.
C BW 96 96
            TETDRFD.
C ET 86 ET
            AETDPYA.
C_IN_93_93
            TKTDPFD.
C_IN_93_93
            AKTDPFA.
C_IN_93_93
            TKTDPFA.
C_IN_94_94
            TTSDPFD.
C_IN_95_95
            TKTDPFD.
CRF01 AE C
            AKTDPFA.
CRF01_AE_C
            AETDPDW.
CRF01_AE_C
            TKTDPCA.
CRF01_AE T AETDOCD.
CRF01 AE T AETDPCD.
CRF01_AE T AETDPCD.
CRF01_AE_T
            AETDPCD.
CRF01_AE_T
            AETDPD..
CRF01_AE_T
            AETDOCD.
CRF02_AG_F
            TETDOGD.
CRF02 AG F
            TKTDPCD.
CRF02 AG G
            TETDPFA.
CRF02 AG N
            TKTDPCD.
CRF02_AG_S
            TETDPCD.
CRF02_AG_S
            TETGPCD.
CRF03 AB R
            TETHPFD.
CRF03 AB R
            TETHPFD.
CRF04_cpx_
            TEADPFA.
CRF04_cpx_
            TEADPFD.
CRF04_cpx_
            TESNPFD.
CRF05 DF B
            TEADQFDW
CRF05_DF_B AETDPFDC
CRF06_cpx_
            AEPDRFD.
CRF06_cpx
            AEPDRFD.
CRF06_cpx
            AETDRFD.
CRF06_cpx_
            TEPDRFD.
CRF11_cpx_ AEPDRFD.
CRF11_cpx_
            AEPAPFD.
D_CD_83_EL AETDPDC.
D_CD_83_ND AETDPFDW
D_CD_84_84
            TEVHPFDW
D_UG_94_94
            TEADPFDW
F1_BE_93_V
            AKTDPCA.
F1_BR_93_9
            AKTDPD..
F1 FI 93 F
            AKTDPCD.
F1 FR 96 M
            TETDPFD.
F2_CM 95 M
            TKTDPSD.
F2KU_BE 94
            TETDPLD.
G_BE_96_DR
            TETDPFD.
G_NG_92_92
            TETDPLD.
```

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G_SE_	93_SE	AEADQCD.
H_BE	VI9	TETDPFDW
H_BE	VI9	TEADPCD.
H_CF_	90_90	TETDPD
J_SE	93_SE	AEPDRFD.
J_SE_	94_SE	AEPDRFD.
K_CD	97_EQ	TKTDPD
K_CM	96 MP	TKTDQFD.
N_CM	95_YB	TEADPCD.
O_CM	ANT	AGPGGYPR
O_CM	91_MV	TGPSGQPC
O_SN_	998	ACP.RYPG
o_sn_	998	TGSDRYPR
U_CD_	83C	TTTDPFD.

Table 17. HIV Vif Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

•					
Name: 00BW0762_1	Len:	194	Check: 4675	Weight:	1.00
Name: 00BW0768_2	Len:	194	Check: 4961	Weight:	1.00
Name: 00BW0874_2	Len:	194	Check: 3755	Weight:	1.00
Name: 00BW1471_2	Len:	194	Check: 3843	Weight:	1.00
Name: 00BW1616_2	Len:	194	Check: 4613	Weight:	1.00
Name: 00BW1686_8	Len:	194	Check: 4096	Weight:	1.00
Name: 00BW1759_3	Len:	194	Check: 3523	Weight:	1.00
Name: 00BW1773_2	Len:	194	Check: 4446	Weight:	1.00
Name: 00BW1783_5	Len:	194	Check: 3151	Weight:	1.00
Name: 00BW1795_6 -	Len:	194	Check: 4892	Weight:	1.00
Name: 00BW1811_3	Len:	194	Check: 3877	Weight:	1.00
Name: 00BW1859_5	Len:	194	Check: 3290	Weight:	1.00
Name: 00BW1880_2	Len:	194	Check: 2555	Weight:	1.00
Name: 00BW1921_1	Len:	194	Check: 4284	Weight:	1.00
Name: 00BW2036_1	Len:	194	Check: 4019	Weight:	1.00
Name: 00BW2063_6	Len:	194	Check: 4165	Weight:	1.00
Name: 00BW2087_2	Len:	194	Check: 5068	Weight:	1.00
Name: 00BW2127_2	Len:	194	Check: 5231	Weight:	1.00
Name: 00BW2128_3	Len:	194	Check: 5469	Weight:	1.00
Name: 00BW2276_7	Len:	194	Check: 5547	Weight:	1.00
Name: 00BW3819_3	Len:	194	Check: 1251	Weight:	1.00
Name: 00BW3842_8	Len:	194	Check: 4197	Weight:	1.00
Name: 00BW3871_3	Len:	194	Check: 3487	Weight:	1.00
Name: 00BW3876_9	Len:	194	Check: 4432	Weight:	1.00
Name: 00BW3886_8	Len:	194	Check: 5175	Weight:	1.00
Name: 00BW3891 6	Len:	194	Check: 3845	Weight:	1.00
Name: 00BW3970_2	Len:	194	Check: 2268	Weight:	1.00
Name: 00BW5031 1	Len:	194	Check: 3711	Weight:	1.00
Name: 96BW01B21	Len:	194	Check: 4602	Weight:	1.00
Name: 96BW0407	Len:	194	Check: 5108	Weight:	1.00
Name: 96BW0502	Len:	194	Check: 4385	Weight:	1.00
Name: 96BW06_J4	Len:	194	Check: 5371	Weight:	1.00
Name: 96BW11_06	Len:	194	Check: 6037	Weight:	1.00
Name: 96BW1210	Len:	194	Check: 4343	Weight:	1.00
Name: 96BW15B03	Len:	194	Check: 5690	Weight:	1.00
Name: 96BW16_26	Len:	194	Check: 4471	Weight:	1.00
Name: 96BW17A09	Len:	194	Check: 3907	Weight:	1.00
Name: 96BWMO1_5	Len:	194	Check: 5608	Weight:	1.00
Name: 96BWMO3_2	Len:	194	Check: 3079	Weight:	1.00
Name: 98BWMC12_2	Len:	194	Check: 5336	Weight:	1.00
Name: 98BWMC13_4	Len:	194	Check: 5304	Weight:	1.00
Name: 98BWMC14_a	Len:	194	Check: 3984	Weight:	1.00
Name: 98BWMO14_1	Len:	194	Check: 2480	Weight:	1.00
Name: 98BWMO18_d	Len:	194	Check: 2801	Weight:	1.00
Name: 98BWMO36_a	Len:	194	Check: 3762	Weight:	1.00
Name: 98BWMO37_d	Len:	194	Check: 4971	Weight:	1.00
Name: 99BW3932_1	Len:	194	Check: 4165	Weight:	1.00
Name: 99BW4642_4	Len:	194	Check: 2912	Weight:	1.00
Name: 99BW4745_8	Len:	194	Check: 5323	Weight:	1.00
Name: 99BW4754_7	Len:	194	Check: 3964	Weight:	1.00
Name: 99BWMC16_8	Len:	194	Check: 6325	Weight:	1.00
Name: A2_CD_97CD	Len:	194	Check: 5849	Weight:	1.00
Name: A2_CY_94CY	Len:	194	Check: 5097	Weight:	1.00
Name: A2D97KR	Len:	194	Check: 3871	Weight:	1.00
Name: A2G_CD_97C	Len:	194	Check: 5705	Weight:	1.00
Name: A_BY_97BL0	Len:	194	Check: 8467	Weight:	1.00

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A_SE_SE853 MENRWQVMIV WQVDRMRIRT WNSLVKHHMY ISKKAKNWFY RHHFESRHPK
A_SE_SE889 MENRWQVMVV WQVDRMRIRT WNSLVKHHMY ISKKAKGWLY RHHFESRHPK
A_SE_UGSE8 MENRWQVMIV WQVDRMRIRT WNSLVKHHMY ISKKAAGWFY RHHYESRHPK
A_UG_92UG0 MENRWQVMIV WQVDRMRIRT WNSLVKHHMY ISRRAKGWFY RHHYESRHPK
            MENRWQVMIV WQVDRMKIRT WNSLVKHHMY VSKKAQGWFY RHHYESRHSR
A UG U455
AC_IN_2130 MENRWQALIV WQVDRMKIRT WNSLVKHHMY VSRKANGWFY RHHYDSRHPK
AC_RW_92RW MENRWQVMIV WQVDRMKIRT WNSLVKHHMY ASRRAKGWFY RHHYESRHPK
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 ACG_BE_VII MENRWQVMVV WQVDRMRIRT WHSLVKHHMY TSKKAKNWCY RHHYESMHPK
 AD SE_SE69 MENRWQVMIV WQVDRMRIRT WKSLVKYHMY VSKQARGWLY RHHYDCLNPK
 AD_SE_SE71 MENRWQVMIV WQVDRMRIKT WNSLVKHHMY VSKKAQNWVY RHHYESRHPR
 ADHK_NO_97 MENRWQVMIV WQVDRMRIRT WHSLVKHHIY VSKKANKWLF RHHYESRHPK
 ADK_CD_MAL MENRWQVMIV WQVDRMRIRT WHSLVKHHMY VSKKAKNWFY RHHYESRHPK
AG_BE_VI11 MENRWQVMIV WQVDRMRIRT WNSLVKHHMY VSKKAKGWFY RHHYESRHPK
 AG_NG_92NG MENRWQVVIV WQVDRMRIRT WNSLVKYHMY KSKKAKDWFY RHHYESRHPK
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 B_AU_VH_AF MENRWQVMIV WQVDRMRIRT WKSLVKHHLY KSGKARRWVY RHHYESTHPR
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B_GB_GB8_A

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B_KR_WK_AF MENRWQVMIV WQVDRMRIKT WKSLVKHHMY ISKKAKEWVY RHHYESTHPR
B_NL_3202A MENRWQVMIV WQVDRMRIRA WKSLVKHHMY KSKKAERWFY RHHYESTHPR
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B_US_BC_LO MENRWQVMIV WQVDRMRIRT WISLVKHHMY ISRKAKGWFY RHHYESTHPK
B_US_DH123 MENRWQVMIV WQVDRMRIRT WKSLVKHHMY VSKKAKGWFY RHHYBSTHPR
B_US_JRCSF MENRWQVMIV WQVDRMRIRT WNSLVKHHMY ISGKAKGWIY KHHYBSTNPR
B_US_MNCG_ MENRRQVMIV WQADRMRIRT WKSLVKHHMY ISKKAKGRFY RHHYESTHPR
B_US_P896 MENRWQVMIV WQVDRMRIRT WKSLVKHHMY ISKKAKGWFY RHHYESTHPR
B_US_RF_M1 MENRWQVMIV WQVDRMRIRT WKSLVKHHMY ISRKAKGWFY RHHYESTHPR
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B_US_YU2_M MENRWQVMIV WQVDRMRIRT WKSLVKHHXH ISGKARGWFY RHHYESTHPR
B_US_YU2_M MENRWQVMIV WQVDRMRIRA WKSLVKHHXH ISGKARGWFY RHHYESPHPR
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C_ET_ETH22 MENRWQVLIV WQVDRMKIRT WNSLVKHHMH ISRRANGWYY RHHYDSRHPK
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CRF02_AG_S MENRWQVMIV WQVDRMRIRT WNSLVKYHMY KSRKAKDWFY RHHYESSHPR
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 B FR HXB2
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           PETADRMIHL HYFTCFTASA VRKAILGORV LTKCEYPTGH SQVGTLQLLA
O CM ANT70
O_CM_MVP51 PETADRMIHL HYFTCFTESA IRKAILGQRV LTKCEYLAGH SQVGTLQFLA
O SN 99SE_
           PETADRMIHI YYFACFTESA IRKAILGQRV LTRCEYPAGH SQVGTLQLLA
            PETADRMIHT YYFACFTESA IRKAILGQRV LTRCEYSAGH SQVGTLQLLA
O_SN_99SE_
U CD 83C PDLADQLIHL HYFDCFSDSA IRKAILGHIV SPRCEYQTGH NKVGSLQYLA
            151
00BW0762_1 LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
00BW0768 2 LTALIKPKKI KPPLPSVRKL VEDRWNKPQR TKGRRGNHTM NGH.
00BW0874_2 LTALIKPHKR KPPLPSVRKL VEDRWNNPQK TKGRRGNHTM NGH.
00BW1471_2 LTALIKPKRI KPPLPSLQKL VEDKWNNPQK TRGHRGSHTM NGH.
00BW1616_2 LTALIKPKKI KPPLPSVRKL VEDRWNNPQK TRGRRGNHTM NGH.
00BW1686_8 LTALIKPKKI KPPLPSIRKL VEDRWNKPQK TRGRRGNHTM NGH.
00BW1759_3 LTALIKPRKI KPPLPSVRKL VEDKWNKPQK TRGRRGNHTM NGH.
00BW1773_2 LTALIKPKKI KPPLPSVRKL VEDRWNNPQK TRGRRGNHTM NGH.
00BW1783_5 LTALIKPKKR KPPLPSVRKL VEDRWNKPPK TRDRRGNHTM NGH.
00BW1795_6 LTALIKPKKR KPPLPSVKKL VEDRWNKPQK TRGRRGSHTM NEH.
00BW1811_3 LTALIKPQRR KPPLPSVSKL VEDRWNNPQK TRGRRGCHTM NGH.
00BW1859_5 LTALIKPKKI KPPLPSVRKL VEDRWNNPQK TRGRRGNHTM NGH. 00BW1880_2 LTALIKPKKI KPPLPSVRKL VEDRWNKPQK TRGRRGNYTM NGH.
00BW1921_1 LTALIKPKKI KPPLPSVQKL VEDRWNKPQK TRGRRGNHTM NGH.
00BW2036_1 LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGRKGNHTM NGH.
00BW2063_6 LTALIKPKKR KPPLPSVRKL VEDRWNNPQK TRGHRGNHTM NGH.
00BW2087_2 LTALVKPKKI KPPLPSVKKL VEDRWNKPQK TRGRRGNHTM NGR.
00BW2127_2 LTALIKPKQI KPPLPSVQKL VEDRWNKPQK TRGRRGDHTM NGH.
00BW2128_3 LTALIKPKKI KPPLPSVKKL VEDRWNNPQK TRGRRGNHTM SGH.
00BW2276_7 LTALIKPKRR KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
00BW3819_3 LTAIK.PKKR KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
00BW3842_8 LTALIKPKKR KPPLPSVRKL VEDRWNKSQK TRDRRGNHTM NGH.
00BW3871_3 LTALIKPKKI KPPLPSIRKL VEDRWNKSQK TRGRRGNHTM NGH.
00BW3876_9 LTALIKPKKI KPPLPSVRKL ABDRWNNPQK TRGRRGNHTM SGH.
00BW3886_8 LTALIKPKKR KPPLPSVRKL VEDRWNNSQK TRDHRGNHTM SGH.
00BW3891_6 LTALIKPKKR KPPLPSVRKL VEDRWNNPQK TRGHRGNHTM NGH.
00BW3970_2 LTTLIKPKRR KPPLPSVRKL AEDRWNNPQK TRDRRGNHTM NGH.
00BW5031_1 LTALIKPKRP KPPLPSVRKL AEDRWNKPRK TRGRRGNHTM NGH.
96BW01B21 LTALIKPKKR KPPLPSVKKL VEDRWNDPQK TRGRRGSHTM NGH.
  96BW0407 LTALIKPKKR KPPLPSVRKL VEDRWNEPQK TRGRRGNHTM NGH.
 96BW0502 LTALIKPKQR KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
96BW06_J4 LTALIKPKKR KPPLPSISKL VEDRWNKPQR TRGRRGNHTM NGH.
 96BW11_06 LTALVKPKKI KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
  96BW1210
           LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGRKGNHTM NGH.
           LTALIKPKQI KPPLPSVRKL VEDRRNKPQK TRGRRGNRTM NGH.
96BW15B03
96BW16_26 LTALIKPKKI KPPLPSVNKL VEDRWNNPQK TRGRRGNHTL NGH.
96BW17A09 LTAVIKPKKI KPPLPSVQKL VEDRWNKPQK TRGHRGSHTM NGH.
96BWMO1_5 LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGRRESHTM NGH.
96BWMO3_2 LTALIKPKRI KPPLPSVRKL TEDRWNKPQK TKGRRGNHTM NGH.
98BWMC12_2 LTALIKPQKR KPPLPSVRKL VEDRWNNPQK TRGRRGNHTM NGH.
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98BWMC13_4 LTALIKPKKR KPPLPSVKKL VEDRWNKPQK TRGRRGSHIM NGH.
 98BWMC14_a LTALIKTKKR KPPLPSVSKL VEDRWNKPQK TRGRRENHTM NGH.
 98BWMO14_1 LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGHRGNHTM NGH.
 98BWM018_d LTALIKPKKI KPPLPSVKKL VEDRWNKPQK TRDRRGNHTM NGH.
98BWMO36_a LTALIKPKRR KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
98BWMO37_d LTALIKPKRR KPPLPSVRKL TEDRWNKPQK TRDHRGNHTM NGH.
99BW3932_1 LTALIKPKKI KPPLPSVQKL VEDRWNKPQK TRGRRGNHTM NGH.
99BW4642_4 LTALIKPKKI KPPLPSIRKL VEDRWNNPQK TRGRRGNHTM NGH.
99BW4745_8 LTALLKTKRR KPPLPSVRKL VEDRWNNPQK TRGHRGNHTM NGH.
99BW4754_7
99BW4754_7
LTALIKPKRI KPPLPSVRKL VEDRWNKPQK TRGHRGNHTM NGH.
99BWMC16_8
LTALIKPKVI KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
A2_CD_97CD
LRALVASTRT KPPLPSVRKL VEDRWNKPQK TRGHRGSHTM NGC.
A2_CY_94CY LKAVVASTRT KPPLPSVRKL VEDRWNKPQK TKGHRGSHTM NGC.
A2D__97KR LKALVGETRT KPPLPSVRKL TEDRWNKPQK TKGHRGSHTM NGH.
A2G_CD_97C LRALVKPTKI KPPLPSVKKL TEDRWNKPQK TRGHRENPTM SGY.
A_BY_97BL0 LKALVTPTRE RPPLPSVRXL TEDRXNKPQK TRGRRXNHTM NXC.
A_KE_Q23_A LKALVTPKKT KPPLPSVRIL TEDRWNKPQK TRGLRESHTM NGC.
A_SE_SE659 LRALVAPRKT KPPLPSVRIL AEDRWNKPQK TRDPRESHTM NGC.
A SE SE725 LKALVTPTRT KPPLPSVRKL AEDRWSKPQK TRGHRGSHTM NGC.
            LKALVTPKKT RPPLPSVRIL AEDRWNKSRK TRGPRGSHTM NGC.
A_SE SE753
            LKALVTPKKI KPPLPSVKKL TEDRWNKPQK TRGHRGNHTM HGY.
A SE SE853
A_SE_SE889 LKALVTPKKI RPPLPSVRKL AEDRWNKPQK TKGHRGSHTM NGH.
A_SE_UGSE8 LKALVTPKRT KPPLPSVRKL TEDRWNKPQK TKGHRGSHTM NGC.
A_UG_92UG0 LKALVTPSRM KPPLPSVKKL AEDRWNKPQK TRGRRESHTM NGC.
A UG U455
            LKALVTPTRA KPPLPSVKKL TEDRWNKPQK TRGHRGSRTL NRH.
AC_IN_2130 LTALIKPKKR KPPLPSIRKL VEDRWNNPQK TRGRRGNHTM NGH.
AC_RW_92RW LTALIKPKKI KPPLPSVSKL VEDKWNKPQK TRGRRGNHTM NGH.
AC_SE_SE94 LTALIKPKKI KPPLPSVRKL VEDKWNKPQK TRGRRGNHTM NGH.
ACD_SE_SE8 LKALVTPTRV KPPLPSVRKL AEDRWSKSQK TRGLRGSLTM NGC.
ACG_BE_VI1 LKALVTPTQI RPPLPSVRKL TEDRWNKPQK TRGHRGNHTM NGH.
            LTALITPKKE KPPLPSVKKL TEDRWNKPQR TKGHRGSHTM NGH.
AD SE SE69
            LKALVTPTKT KPPLPSVRIL TEDRWNKPQK TRGLRESHTM NGC.
AD SE SE71
            LTALVAPKKI KPPLPSIKKL AEDRWNKPQK TRGHRGSHTM NGC.
ADHK NO 97
ADK_CD_MAL LTALIAPKKT RPPLPSVRKL TEDRWNKPQQ TKGHRGSHTM NGH.
AG_BE_VII1 LKALVTPTRI RPPLPSVRKL TEDRWNKPQK TRGHRGSHTM NGQW
AG_NG_92NG LKALVTPTQT KPPLPSVKKL TEDRWNEPQK TRGHRGSHST NGH.
AGHU_GA_VI LKALVTPTRE RPPLPSVQKL TEDRWNKPQK TKDHRGSHTM NGC.
AGU_CD_Z32 LTALITPKKT KPPLPSVKKL VEDRWNKPQK TRGHRENQTM NEH.
AJ_BW_BW21 \LKAILKTEKR KPPLPSVQKL VEDRWNKPQR TRGHRESHTM NGH.
            LAALITPROT KPPLPSVTKL TEDRWNKPRK TKGHRGSHTM SGH.
B_AU_VH_AF
B CN RL42
            LTALTTPKNR KPPLPSVTKL TEDRWNKPQR TKGHRGSHTM SGH.
           LAALITPKKI KPPLPSVAKL TEDRWNKPRK TKGHRGSHTM NGH.
B_DE_D31_U
B_DE_HAN_U LAALTTPKKI KPPLPIVTKL TEDRWNKPQK TKGHRGSHTM HGH.
B FR HXB2
            LAALITPKKI KPPLPSVTKL TEDRWNKPQK TKGHRGSHTM NGH.
B GA OYI_
            LAALIKPKKI KPPLPSVTKL TEDRWNKPQK TKGHRGSHTM NGH.
B GB CAM1
            LTALIAPKKI KPPLPSVRKL TEDRWNKPQK TKGHRGSHTM NGH.
B_GB_GB8_A LTALITPKKI KPPLPSVTKL TEDRWNKPQK TKGHRGSHTM NGH.
           LAALITPKKT KPPLPSVTKL TEDRWNKPQK TKGHRESHTM NGH.
B GB MANC
B_KR_WK_AF LTALITPKKI KPPLPSVRKL TEDRWNKPQK TKGHRGSHTM NGH.
B_NL_3202A LAALIKPKKI KPPLPSVTKL TEDRWNKPQK TKGHRGSHTM NGH.
B_TW_TWCYS LTALVQPKKI KPPLPSVVKL TEDRWNKPQK TKGHRGSHTM HGH.
B_US_BC_L0 LAALITPKRI KPPLPSVTKL TEDRWNKPQK TKGHRGSHTM NGH.
            LAALVTPRKI KPPLPSVAKL TEDRWNKSHK TKGHRGSHTM NGH.
B US DH123
            LTALIKPKKI KPPLPSVKKL TEDRWNKPQK TKGHRGSHTM NGH.
B US JRCSF
            LTALITPKKI KPPLPSVKKL TEDRWNKPQK TKGHRGSHTI NGH.
B_US_MNCG_
B US P896
            LAALTTPRRI KPPFPSVTKL TEDRWNKPQK TKGHRGSHTM TGH.
B_US_RF_M1 LAALTTPKKI KPPLPSVKKL TEDRWNKPQK TKGHRGSHTM NGH.
B_US_SP2_K LAALITPKKT KPPLPSVKKL TEDRWNKPQK TKGHRGSHTM NGH.
B_US_WEAU1 LTALITPKKI KPPLPSVKKL TEDRWNKPQK TKGHRGSHTM NGH.
B_US_WR27_ LTALIKPXKI KPPLPSVKKL TEDRWNXPQK TKGHRGSHTM NGH.
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B_US_YU2_M LTALITPKKT KPPLPSVKKL TEDRWNKPQK TKGHRGSRTM NGH.
 BF1_BR_93B LTALIKPKKR KPPLPSVKKL TEDRWNKPQK TKDHRGSHTM NGH.
 C_BR_92BR0 LTALIKPKKI KPPLPSVKKL VEDRWNKPQK TRDRRGNHTM NGH.
 C_BW_96BW0 LTALIKPKKR KPPLPSVRKL VEDRWNEPQK TRGRRGNHTM NGH.
 C_BW_96BW1 LTALIKPKKI KPPLPSVRKL VEDRWNKPQK TRGRRGNHTM NGH.
 C_BW_96BW1 LTALIKPKKR KPPLPSVRKL VEDRWNKPQK TRGRKGNHTM NGH.
 C_BW_96BW1 LTALIKPKQI KPPLPSVRKL VEDRRNKPQK TRGRRGNRTM NGH.
 C_ET_ETH22 LTALIKPKKA KPPLPSVSKL VEDKWNKPQK TRGRRGNHTM NGH.
C_IN_93IN1 LTALIKPKKI KPPLPSIKKL VEDRWNNPQK IRGRRGNHTM NGH.
             LTALIKPKKI KPPLPSIKKL VEDRWNNPQK IRGRRGNHTM NGH.
 C_IN_93IN9
 C_IN_93IN9 LTALIKPKKI KPPLPSVRKL VEDRWNNPLK TRGRRGNHTM NGH.
 C_IN_94IN1 LTALIKPKKI KPPLPSIKKL VEDRWNNPQK IRGRRGNHTM NGH.
 C_IN_95IN2 LTALIKPKKI KPPLPSIKKL VEDRWNNPQK IRGRKGNHIM HGH.
 CRF01_AE_C LKALATPKKT RPPLPSVRKL TEDRWNKPQK TRGHRENPTM NGH.
 CRF01_AE_C LKALTKTKKT KPPLPSVRKL TEDRWNKPQK TKGHRESPTM NGH.
 CRF01_AE_C LKALATPKKI RPPLPSVRKL TEDRWNKPQK TRGHRENPTM SGH.
 CRF01_AE_T LKALTTPKRI RPPLPSVKKL TEDRWNKPQK IWGHRENPTM NGH.
 CRF01_AE_T LKALTTPKRI KPPLPSVKKL TEDRWNKPQK IRDHREYRTM NGH.
 CRF01_AE_T LKALTTPKRI RPPLPSVKKL TEDRWNKPQK IKGHRENPTM NGH.
 CRF01_AE_T LKALTTPKRI RPPLPSVKKL TEDRWNKHQ. KGDHRENPTM NGH.
 CRF01_AE_T LKALTTPKRI RPPLPSV.EI TEDRWNKPQ. KRGHRENPTM NGH.
 CRF01_AE_T LKALTTPKRI KPPLPSVRKL TEDRWNEPQK IRGHREYPTM NGH.
 CRF02_AG_F LKALVTPAKT KPPLPSVKKL AEDRWNKPQK TRGHRGNRSM NGH.
 CRF02_AG_F LKALVTPVKT KPPLPSVKKL AEDRWNKPQK TRGHRGNRSM NGQ.
CRF02_AG_G LKALVTPTRK KPPLPSVRKL AEDRWNEPQK TRGHRGSRPM NGR.
CRF02_AG_N LNALVAPTKT KPPLPSVRKL AEDRWKEPQK TRGHRGSRPM NGH.
CRF02_AG_S LKALVTPTRT KPPLPSVKKL AEDRWNEPQK TRGHRGSRSM NGH.
CRF02_AG_S LKALVTPTRR KPPLPSVKKL AEDRWNEPQK TRGHRGNRSM NGH.
CRF03_AB_R LAALRTPKKI KPPLPSVTKL TEDRWNKPQR TKDHRGSHTM SGH.
CRF03_AB_R LAALRTPKKI KPPLPSVTKL TEDRWNKPQR TKDHRGSHTM SGH.
CRF04_cpx_ LAALISPKKT KPPLPSVKKL VEDRWNKPOK TRGRRENOIM NGH.
CRF04_cpx_
            LAALISPKKT KPPLPSVKKL VEDRWNKPQK TRGRRENQIM NGH.
            LAALISPKKT KPPLPSVKKL VEDRWNKSQK TKGRRESHIM NGH.
CRF04 cpx
CRF05 DF B LTALITPKKT KPPLPSVRKL TEDRWNKPQK TKGRRGNHTM NGY.
CRF05_DF_B LTALITPQKI KPPLPSVRKL TEDRWNKPQR TKGHRGCHTM NGY.
CRF06_cpx_ LTALIKPEKR KPPLPSVQKL VEDRWNKPQK TRGHRESHTM NGH.
CRF06_CPX_ LTALIKPKKR KPPLPSVQKL VEDRWNKPQK TRDHRESHTM NGH.
CRF06_cpx_
            LTALIKPRKR KPPLPSVQKL VEDRWNKPQK TRDHRECHTM NGH.
            LKALVKTKRR KPPLPSVQKL VEDRWNKPQK TKDHRESHIM DGH.
CRF06_cpx_
            LKALVTPTRA KPPLPSVRKL AEDRWNKPQK TRGHRGNHTA NGC.
CRF11_cpx_
CRF11_CPX_ LKALVTPKRT KPPLPSVRKL TEDRWNKPQK TRGRRGNHTV NGC.
D_CD_84ZR0 LTALIAPKKR KPPLPSVKKL TEDRWNKPRQ TKGRRGSHTM NGH.
D_CD_ELI_K LTALIAPKQI KPPLPSVRKL TEDRWNKPQQ TRGHRGSHTM NGH.
D_CD_NDK_M LAALIAPKKI KPPLPSVRKL TEDRWNKPQK TKGRRGSHTM NGH.
D_UG_94UG1 LTALVTPRKI KPPLPSVGKL TEDRWNKPQR TKGHRGSHTM NGH.
F1_BE_VI85 LTALIAPEKT KPPLPSVQKL VEDRWNKPQE TRGHRGSHTM NGH.
F1_BR_93BR LTALIAPKKT KPPLPSVQKL VEDRWNKPQK TRGHRESHTM NGH.
F1_F1_FIN9 LTALVSPKKA KPPLPSVKKL VEDRWNKPQR IRGHRGSHTM NGH.
F1_FR_MP41 LTALIAPKKT KPPLPSVKKL VEDRWNKPQB TRGHRGSHTM NGH.
F2_CM_MP25 LTALITPKKI KPPLPSVRKL VEDRWNNPQK TRGHRGSHTM NGH.
F2KU_BE_VI LTALVAPKKT KPPLLSVRKL VEDRWNKPQK TRDHRGSHTM NGH.
G_BE_DRCBL LKVLVAPTRR RPPLPSVRKL TEDRWNEPQK TRGHRENPTM NGH.
G_NG_92NG0 SKALVTPTRK RPPLPSVGKL AEDRWNKPQK TRDHRENPTM NGH.
G SE SE616
            LKVLVTSKRS RPPLPSVTEL AEDRWNKPQK TRGHRENPTM NGH.
H_BE_VI991 LTALISPKRT KPPLPSVRKL VEDRWNKPQK TRGHRGSHTM NGH.
H_BE_VI997 LTALVAPKKT KPPLPSVKKL VEDGWNKPQK TRGHRGSHTM NRH.
H_CF_90CF0 LTALVAPKKI KPPLPSVRKL VEDRWNKPQK TRGHRGSHTM NGH.
J_SE_SE702 LTALIKPKRR KPPLPSVQKL VEDRWNKPQK TRDHRESHTM NGH.
J_SE_SE788 LTALIRPKRR KPPLPSVQKL VEDRWNKPQK TTGHRESHTM NGH.
K_CD_EQTB1 LTALIAPKKT KPPVPSVQKL VEDRWNKPQK TRGHRGSHTM SGQ.
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SOMSHOES DEERDE

K CM MP535	LTALVAPRRP	KPPVPSVKKL	VEDRWNKPOK	TRCHRGSOTM	NGH
N CM YBF30	LTAWVGAKKR	KPPLPSVTKL	TEDDMMEROK	MOCURCURATION	NOII.
O CM ANT70	TDVIVIKADED	KPPLPSVQKL	TEDRINGIUM D	TDDOL VODOM	NGH.
O CM MVP51	T ICA LO LO COLLO	KEFLESVOKU	TEDRWINNILR	IRDQLKSPSM	NGH.
	LKAVVKVKRN	KPPLPSVQRL	TEDRWNKPWK	IRDQLGSHSM	NGH.
O_SN_99SE_	LRVVVKEKRN	KPPLPSVQKL	TEDRWSRHLR	IRDQLESHSM	NGH.
O_SN_99SE_	LRVVVKEKRH	KPPLPSVQKL	TEDRWSRHLR	IRDQLGSHSM	NGH.
U_CD83C	LTTLVAPTKR	KPPLPSVRKL	VEDRWNKPQK	TKGHKGSHTM	HGH.

Table 18. HIV Vpr Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

Name:	_	Len:	100	Check: 8179	Weight:	1.00
Name:	——————————————————————————————————————	Len:	100	Check: 8119	Weight:	1.00
Name:		Len:	100	Check: 7661	Weight:	1.00
Name:	00BW1471_2	Len:	100	Check: 6614	_	1.00
Name:	00BW1616_2	Len:	100	Check: 6361	_	1.00
Name:	00BW1686_8	. Len:	100	Check: 6014	Weight:	1.00
Name:	00BW1759_3	Len:	100	Check: 6894	Weight:	1.00
Name:	00BW1773 2	Len:	100	Check: 7772	Weight:	1.00
Name:	00BW1783_5	Len:	100	Check: 7149	_	1.00
Name:	00BW1795_6	Len:	100	Check: 7614	Weight:	1.00
Name:	00BW1811 3	Len:	100	Check: 7968	Weight:	1.00
Name:	00BW1859 5	Len:	100	Check: 6222	Weight:	1.00
Name:	00BW1880 2	Len:	100	Check: 6941	Weight:	1.00
Name:	00BW1921 1	Len:	100	Check: 8183	Weight:	1.00
Name:	00BW2036 1	Len:	100	Check: 8175	Weight:	1.00
Name:	00BW2063 6	Len:	100	Check: 8705	Weight:	
Name:	00BW2087 2	Len:	100	Check: 7388	Weight:	1.00
Name:		Len:	100	Check: 8282		1.00
Name:	_	Len:	100	Check: 8282	Weight:	1.00
Name:	_	Len:	100	Check: 6468	Weight:	1.00
Name:	_	Len:	100	Check: 5670	Weight:	1.00
Name:	· · · · · -	Len:	100		Weight:	1.00
Name:		Len:	100		Weight:	1.00
Name:		Len:	100		Weight:	1.00
Name:		Len:	100		Weight:	1.00
Name:		Len:			Weight:	1.00
Name:	- · · · · - ·	Len:	100		Weight:	1.00
Name:		Len:	100 100	Check: 7113	Weight:	1.00
Name:		Len:		Check: 5511	Weight:	1.00
Name:			100	Check: 7551	Weight:	1.00
Name:		Len:	100	Check: 8226	Weight:	1.00
Name:	96BW06 J4	Len:	100	Check: 8242	Weight:	1.00
Name:	96BW11 06	Len:	100	Check: 7544	Weight:	1.00
Name:	96BW1210	Len:	100	Check: 7942	Weight:	1.00
Name:	96BW15B03	Len:	100	Check: 8580	Weight:	1.00
Name:	96BW16 26	Len:	100	Check: 7308	Weight:	1.00
Name:	96BW17A09	Len:	100	Check: 7009	Weight:	1.00
Name:		Len:	100	Check: 6492	Weight:	1.00
Name:	96BWMO1_5	Len:	100	Check: 5837	Weight:	1.00
Name:	96BWMO3_2	Len:	100	Check: 5277	Weight:	1.00
	98BWMC12_2	Len:	100	Check: 7807	Weight:	1.00
Name:	98BWMC13_4	Len:	100	Check: 9051	Weight:	1.00
Name:	98BWMC14_a	Len:	100	Check: 7867	Weight:	1.00
Name:	98BWMO14_1	Len:	100	Check: 7266	Weight:	1.00
Name:	98BWMO18_d	Len:	100	Check: 7638	Weight:	1.00
Name:	98BWMO36_a	Len:	100	Check: 7495	Weight:	1.00
Name:	98BWM037_d	Len:	100	Check: 6640	Weight:	1.00
Name:	99BW3932_1	Len:	100	Check: 6974	Weight:	1.00
Name:	99BW4642_4	Len:	100	Check: 6081	Weight:	1.00
Name:	99BW4745_8	Len:	100	Check: 8860	Weight:	1.00
Name:	99BW4754_7	Len:	100	Check: 6856	Weight:	1.00
Name:	99BWMC16_8	Len:	100	Check: 8223	Weight:	1.00

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00BW0762_1 MEQAPEDQGP QREPYNEWTL BLLEBLKQEA VRHFPRPWLH SLGQHIYNTY
 00BW0768_2 MEQAPEDQGP QREPYNEWTL BILBELKQEA VRHFPRPWLH NLGEYIYETY
 00BW0874_2 MEQPPEDQGP QREPYNEWTL BILEBLKQEA VRHFPRPWLH SLGQYIYETY
 00BW1471_2 MEQPPEDQGP QREPYNEWTL BLLEBLKQEA VRHFPRPWLH SLGQHIYETY
 00BW1616_2 MEQPPEDQGP QREPYNEWTL BLLEBLKQEA VRHFPRPWLH SLGQYIYENY
 00BW1686_8 MEQAPEDQGP QREPYNEWAL EILEELKQEA VRHFPRPWLH SIGQYIYETY
 00BW1759_3 MEQAPEDQGP QREPYNEWTL BLLEBLKQEA VRHFPRPWLH GLGQHIYETY
 00BW1773_2 MEQPPEDQGP QREPYNEWTL ELLEELIQEA VRHFPRPWLH SLGQYIYETY 00BW1783_5 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SMGQHIYNTY
 00BW1795_6 MEQAPEDQGP QREPYN.ETL ELLEBLKQEA VRHFPRIWLH NLGQYIYNTY
 00BW1811_3 MEQPPEDQGP QRVPYNEWAL ELLEELKQEA VRHFPRPWLH GLGQYVYETY
 00BW1859_5 MEQPPEDQGP QREPYNEWAL EILBELKQEA VRHFPRLWLH SLGQYIYETY
 00BW1880_2 MEQAPEDQGP QRELYNEWTL ELLEELKQEA ARHFPSSWLH GLGQHIYNTY
00BW1921_1 MEQAPEDQGP QREPYNEWTL ELLBELKQEA VRHFPRTWLH NLGQYIYQTY
00BW2036_1 MEQAPEDQGP QREPYNEWTL EILBELKQEA VRHFPRPWLQ SLGQYIYETY
00BW2063_6 MEQPPEDQGP QREPYNEWTL GLLEELKQEA VRHFPRLWLH NLGQYIYNTY
00BW2087_2 MEQAPEDQGP QREPYNEWAL ELLEELKQEA VRHFPRPWLH NLGQYIYETY
00BW2127_2 MEQAPEDQGP QRGPYNEWTL EILEELKQEA VRHFPRPWLH NLGQYIYETY
00BW2128_3 MEQPPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH GLGQYIYETY
00BW2276_7 MEQTPEDQGP QREPYNEWAL EILEELKQEA VRHFPRTWLH SLGQYIYDTY
00BW3819_3 MEQAPEDQGP QREPYNEWTL EILEBLKQGA VRHFPRPWLH NLGQHIYETY
00BW3842_8 MEQVPEDQGP QREPYNEWTL EILEBLKQEA VRHFPRPWLQ GLGHYIYETY
00BW3871_3 MEQVPEDQGP QREPYNEWTL EILBELKQEA VRHFPRPWLH NLGQYIYETY
00BW3876_9 MEQSPEDQGP QREPYNEWTL ELLEBLKQEA VRHFPRPWLH GIGQYIYETY
00BW3886_8 MEQFPEDQGP QREPYNEWTL ELLEELKQEA VKHFPRPWLH NLGQHIYETY
00BW3891_6 MEQPPEDQGP QREPYNEWTL EVLERLKQEA VRHFPRPWLH SLGQYVYETY
00BW3970_2 MEQPPEDQGP QREPYNEWAL EILEBLKQEA VRHFPRPWLH SLGQHIYETY
00BW5031_1 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SLGQHIYETY
96BW01B21 MERPPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH GLGQYIYETY
96BW0407 MERAPEDQGP QREPYNEWAL ELLEELKQEA VRHFPRMWLH GLGQYIYETY
96BW0502 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPGPWLH GLGQYVYETY
 96BW06_J4 MEQAPEDQGP QREPYNEWTL EILEELKQEA VRHFPPPWLH SLGQYIYETY
 96BW11_06 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SLGQHIYNTY
  96BW1210 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SLGQYIYETY
 96BW15B03 TEQAPEDQGP QREPYNEWAL EILEELKQEA VRHFPRPWLH SLGQYIYETY
 96BW16_26 MEQPPEDQGP QREPYTEWAL ELLEELKQBA VRHFPRPWLH GLGQYIYDTY
 96BW17A09 MEQTPEDQGP QREPHNEWTL ELLEELKQBA VRHFPRPWLH SLGQHIYETY
 96BWMO1_5 MEQAPEDQGP QREPYNEWTL ELLEELKQBA VRHFPR.TLH DLGQHIYNTY
 96BWMO3_2 MEQAPEDQGP QREPYNEWTL EILEELKQEA IRHFPIPYLQ HLGQYIYETY
98BWMC12_2 MEQPPEDQGP QREPYNEWTL EILEELKQEA VRHFPRPWLH SLGQYIYETY
98BWMC13_4 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRIWLH NLGQYVYNTY
98BWMC14_a MEQAPEDQGP QREPYNEWTL EILEELKQEA VRHLPRPWLH SLGQHIYETY
98BWMO14_1 MEQAPEDQGP QREPYNEWTL ALLEDLKQEA VRHVPRPWLH SLGQHIYETY
98BWMO18_d MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SLGQYIYETY
98BWMO36_a MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPITWLH NLGQYIYETY
98BWMO37_d MEQAPEDQGP QREPYNEWTL EILEELKQEA VRHFLRPWLH DLGQYIYETY
99BW3932_1 MEQAPEDQGP QREPYNEWTL EILEELKQEA VRHFPRPWLH NLGQYIYATY
99BW4642_4 MEQPPEDQGP QREPYNEWAL EILEELKQEA VRHFPRPWLH NLGQYIYETY
99BW4745_8 MEQPPEDQGP QREPYNEWTL EVLEDLKQEA VRHFPRPWLH SICQYVYSTY
99BW4754_7 MEQAPENQGP QREPYNEWAL ELLEELKQEA VRHFPRPWLH DLGQHIYNTY
99BWMC16_8 MEQAPEDQGP QREPYNEWTL ELLEELKQEA VRHFPRPWLH SLGLYIYETY
00BW0762_1 GDTWTGVEAI IRILQQLLFI HFRIGCQHSR IGIMRQ.... RRTRNGASRS
00BW0768_2 GDTWTGVEAL IRVLQQLLFI HFRIGCSHSR IGIVRQ.... RRARNGSSRS
00BW0874_2 GDTWTGVETI IRTLQQLLFI HFRIGCQHSR IGILRQ.... KRARNGASRS
00BW1471_2 GDTWAGVEAL LRILQQLLFI HFRIGCQHSR IGIIPQ.... RRARNGSRRS
00BW1616_2 GDTWAGVEAI TRILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGANRS
00BW1686_8 GDTWTGVEAL MRILQQLLFI HFRIGCQHSR IGILQR.... R.ARNGASRS
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00BW1759 3 GDTWTGVEAI IRILQQLLFI HYRIGCQHSR IGIVRQ.... RRARNGANRS
00BW1773 2
            GDTWTGVEAI IKILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGASRS
           GDTWAGVEAI IRILQQLLFI HFRIGCQHSR IGILRQ.... RRTRNGASRS
00BW1783 5
           GDTWTGVEAI IRTLQQLLFV HFRIGCQHSR IGIMRQ.... RRARNGTSGS
00BW1795 6
           GDTWTGVEAI IRILQQLLFV HFRIGCQHSR IGILQQ.... RRARNGASRS
00BW1811_3
00BW1859_5 GDTWAGVEAL IRILQQLLFI HFRIGCQHSR IGILQQ.... RRARNGASRS
00BW1880_2
           GDTWTGVEVL IRILQQLLFI HFRIGCQHSR IGIIRQ.... RRTRNGASRP
00BW1921_1
           GDTWTGVEAL IRILQQPLFI HFRIGCQHSR IGITLP.... RRARNGANRS
           GDTWTGVEAI IRILQQLLFI HFRSGCAHSR IGTLPQ.... RRARNGASRS
00BW2036_1
           GDTWTGVEAI IRILQQLLFI HFRIGCQHSR IGIIRQ.... RRTRNGDSRS
00BW2063 6
00BW2087 2
           GDTWTGVEAL IRILQQLLFT HYRFGCQHSR IGILQQ.... RRARNGANRS
00BW2127 2
           GDTWTGVEVI IRILQQLLFI HFRIGCQHSR IGILRQ.... RRTRNGASRS
           GDTWAGVESL IRMLQHLLFI HFRIGCQHSR IDX.....
00BW2128 3
           CDTWAGVEAI IRILQQLLFT HFRIGCHHSR IGILRQ.... RRARNGASRS
00BW2276 7
           GDTWAGVEAL LRILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGASRP
00BW3819 3
           GDTWTGVETI IRILQQLLFI HFRIGCSRSR IGPMRQ.... RRARNGASRS
00BW3842 8
00BW3871_3
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00BW3876_9
           GDTWTGVEAI IRILQQLLFI HYRIGCAHSR IGIVRQ.... RRARNGANRS
00BW3886_8
           GDTWTGVEAI IRMLQQLLFI HFRIGCQHSR IGILRQ.... RRARNGANRS
00BW3891 6
           GDTWTGVEAL IRMLQQLLFI HFKIGCQHSR IGILRR.... RRARNGASRS
           GDTWTGVEAL IRILQQLLFI HFRIGCQHSR IGIILQ.... RRTRNGASRS
00BW3970 2
00BW5031_1 GDTWMGVEAL IRILQ..... HFRIGCQHSR IGIILQ.... RRTRNGASRS
 96BW01B21 GDTWTGVENM IRILQQLLFV HFRIGCQHSR IGILQQ.... RRARNGASRS
  96BW0407 GDTWTGVEAL IRTLQQLLFI HFRIGCQHSR IGILRQ.... RRVRNGTNRS
  96BW0502 GDTWTGVETL IRILQQLLFI HFRIGCQHSR IGILRQ.... RRTRNGASRS
           GDTWTGVETI IRILQQLLFI HFRIGCQHSR IGILQQ.... RRARNGASRP
 96BW06 J4
 96BW11_06 GDTWTGVEAI IRILQQLLFI HFRIGCQHSR IGIIRQ.... RRTRNGASRP
  96BW1210
           GDTWTGVEVL TRILQQLLFI HFRIGCQHSR IGILRQ.... RRTRNGASRS
 96BW15B03 GDTWTGVEAI IRILQQLLFI HFRIGCLHSR IGIMRQ.... RRARNGASRS
 96BW16 26
           GDTWTGVEIK IRILQQLLFI HFRIGCQHSR IGILQQ.... RRARNGARRS
           GDTWAGVEAL LRILQQLLFI HFRIGCHHSR IGITPQ.... RRARNGSRRS
 96BW17A09
           GDTWTGVEAI TRILQQLLFI HYRIGCQHSR IGIMRQ.... RRARNGASRS
 96BWM01 5
 96BWM03 2
           GDTWAGVLAI IRILQQLLFI HFRIGCSHSR IGIWR..... RRARNGASRS
98BWMC12 2
           GDTWTGVEAI LRILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGASRS
98BWMC13 4
           GDTWTGVEAI IRILQQLLFI HFRIGCQHSR IGILRQ.... RRTRNGASRS
98BWMC14 a
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           GDTWTGVEAI IRILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGANRS
98BWM014 1
98BWM018_d
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98BWM036_a
           GDTWTGVEAL IRTLQQLLFI HFRIGCQHSR IGILRQ.... RRARNGASRS
           GDTWTGVETI IRVLQQLLFI HFRIGCH.SR IGIVRQ.... RRARNGASRS
.98BWM037_d
99BW3932_1
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99BW4642 4
           GDTWAGVEAI IRVLQQLLFI HFRIGCHHSR IGIMQQ.... RRARNGASRS
           GDTWTGVEAL MRILQQLLFI HFRIGCRHSR IGILRQ.... RGARNGASRS
99BW4745 8
99BW4754 7 GDTWTGVEAI IRILQQLLFI HFRIGCHHSR IGIIRQ.... RRTRNGASRP
99BWMC16_8 GDTWTGVEVI IRILQQLLFI HFRIGCQHSR IGILRQ.... RRARNGPSRS
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Table 19. HIV Vpu Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

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Name:	00BW1471_2	Len:	106	Check: 7341	Weight:	1.00
Name:	———	Len:	106	Check: 3870		1.00
Name:		Len:	106	Check: 8787	Weight:	1.00
Name:	00BW1759_3	Len:	106	Check: 7584	Weight:	1.00
Name:		Len:	106	Check: 7507	Weight:	1.00
Name:	00BW1783_5	Len:	106	Check: 7874	Weight:	1.00
Name:	00BW1795_6	Len:	106	Check: 8721		1.00
Name:		Len:	106 -	Check: 3657		1.00
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Name:	00BW1880_2	Len:	106	Check: 5827	Weight:	1.00
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Name:		Len:	106	Check: 6145	Weight:	1.00
Name:	00BW2063_6	Len:	106	Check: 7187		1.00
Name:		Len:	106	Check: 9545	Weight:	1.00
Name:		. Len :	106	Check: 4898		1.00
Name:	00BW2276_7	Len:	106	Check: 7311		1.00
Name:		Len:	106	Check: 4879		1.00
Name:	 -	Len:	106	Check: 1804		1.00
	00BW3871_3	Len:	106	Check: 6650	J	1.00
Name:	00BW3876_9	Len:	106	Check: 6684	3	1.00
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Name:	00BW3891_6 00BW3970_2	Len:	106	Check: 8544		1.00
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Name:	96BW01B21	Len:	106	Check: 7778		1.00
Name:	96BW0407	Len:	106	Check: 6481		1.00
Name:	96BW0502	Len:	106	Check: 4225		1.00
Name:	96BW06 J4	Len: Len:	106	Check: 5292	3	1.00
Name:	96BW11 06	Len:	106	Check: 5367		1.00
Name:	96BW1210	Len:	106	Check: 6477		1.00
Name:	96BW15B03	Len:	· 106 106	Check: 6400		1.00
Name:	96BW16_26	Len:	106	Check: 2981		1.00
Name:	96BW17A09	Len:	106	Check: 5352 Check: 6778		1.00
Name:	96BWM01 5	Len:	106		ب	1.00
Name:	96BWMO3_2	Leń:	106	Check: 5954 Check: 6334	_	1.00
Name:	98BWMC12 2	Len:	106	Check: ,6905		1.00
Name:	98BWMC13_4	Len:	106	Check: 7458	-	1.00
Name:	98BWMC14_a	Len:	106	Check: 4023		1.00
Name:	98BWM014 1	Len:	106	Check: 5708	J	1.00
Name:	98BWM018 d	Len:	106	Check: 7741	Weight:	1.00
Name:	98BWMO36_a	Len:	106	Check: 5445		1.00
Name:		Len:	106	Check: 8225	Weight:	1.00
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Name:	_	Len:	106	Check: 3424	Weight:	1.00
Name:	99BW4754 7	Len:	106	Check: 5468		
Name:		Len:	106	Check: 6656		1.00 1.00
Name:	A2_CD_97CD	Len:	106	Check: 6086	_	1.00
	A2_CY_94CY	Len:	106	Check: 4609	3	1.00
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Name:	A2G_CD_97C	Len:	106	Check: 4405	Weight:	1.00
Name:	A_BY_97BL0	Len:	106	Check: 913	Weight:	1.00
Name:	A_KE_Q23_A	Len:	106	Check: 3380	Weight.	1.00
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                         Len:
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                                                    Weight:
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Name: AC IN 2130
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                        Len:
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                                     Check: 6889
                                                   Weight:
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 Name: CRF01 AE T
                        Len:
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                                                 Weight:
                                                           1.00
 Name: CRF01 AE T
                        Len:
                               106
                                    Check: 2300
                                                 Weight:
                                                           1.00
 Name: CRF01_AE_T
                        Len:
                              . 106
                                    Check: 2481
                                                 Weight:
                                                           1.00
 Name: CRF02 AG F
                        Len:
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                                                           1.00
 Name: CRF02_AG_F
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                                                 Weight:
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                        Len:
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                                                          1.00
 Name: CRF02 AG N
                        Len:
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 Name: CRF02 AG S
                        Len:
                               106
                                    Check: 5296
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 Name: CRF02 AG S
                        Len:
                               106
                                    Check: 4213 Weight:
                                                           1.00
 Name: CRF03 AB R
                        Len:
                               106
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                               106
                                    Check: 8606
                                                 Weight:
                                                           1.00
 Name: CRF04_cpx_
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                                   Check: 5826
                                                 Weight:
                                                           1.00
 Name: CRF05_DF_B
                                   Check: 5193
                        Len:
                               106
                                                 Weight:
                                                           1.00
 Name: CRF05_DF_B
                        Len:
                               106 Check: 5092
                                                 Weight:
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 Name: CRF06_cpx_
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                        Len:
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         00BW1811 3
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00BW2036_1
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        A BY 97BL0
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        A SB SE889
A_SE_UGSE8
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A UG U455
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AC SE ŞE94
ACD_SE_SE8
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ADK CD MAL
    AG_BE_VI11
AG NG 92NG
     AGHU GA VI
     AGU CD Z32
     AJ_BW BW21
    B AU VH AF
B CN RL42
    B DE D31 U
     B DE HAN U
B_FR_HXB2
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B_GA_OYI_M
B_GB_CAM1_
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    B GB GB8 A
B GB MANC
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B_KR WK AP
    ...... .. MQPLVVAA IVA..LVVVA IIAIVVWSIV FIEYRKILRQ
B NL 3202A
B TW TWCYS
    B US BC LO
    B_US_DH123
B_US_JRCSF
    B_US_MNCG_
B_US_P896_
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    B_US_SF2_K
    B US WEAU1
    B US WR27
    B_US YU2 M
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C_ET_ETH22
    C IN 93IN1
    C_IN_93IN9
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    C_IN_95IN2
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CRF01_AE_T
    CRF01_AB_T
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    CRF01_AE_T
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    CRF02_AG_S
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    CRF03_AB_R
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       ..... .... MSDLLA VAIAAFIVAL IIAIVVWTIV YLEYRKLVRQ
CRF05_DF_B
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       D CD ELI K
       D CD NDK M
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       G BE DRCBL
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H_BE_V1991
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       K CD EQTB1
K CM MP535
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N CM YBF30
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       O SN 99SE
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A BY 97BLO
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           RKIDW....L IKRIRERAED SGNESDGD.T EEL....STM VDMGHLRLLD
AC SE SE94
ACD_SE_SE8 KKIDR...L IERIRERAED SGNESDGD.T EEL....AAL VEMGNYDPGD
ACG_BE_VI1 RKIDW....L VKRIRERAED SGNESEGD.T EEL....STM VDMGELRLMD
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B DE HAN U
            RKIDR....L IDRLIERAED SGNESEGEIS ALV....EMG VEMGHHAPWD
B FR HXB2
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B GA OYI M
            KQVDR...L IDRIIERAED SGNESEGD.Q EEL....SAL MEMGHNAPWD
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B US P896
            RKIDR....L IDRIREREED SGNESEGD.Q EEL....AAL ERG.HLAPWD
            KKIDR....L IDRIRERAED SGNESDGD.E EEL....SAL VEMGHHAPWD
B US RF M1
            R.IDR....L IDRIREKAED SGNESEGD.Q EEL....SAL VEMGHLAPWD
B US SF2 K
B_US_WEAU1
            RKIDR....L IDRIRDRAED SCNESEGD.Q EEL....SAL VEMGHHAPWD
B_US_WR27
            RKIDR....L IDRIRERAED SGNESEGD.Q EEL....SAL MEMGHHAPWD
            RKIDR....L INRITERAED SGNESDGD.Q EEL....SAL VERGHLAPWD
B_US_YU2_M
            RKINR....L YKRIRERAED SGNESEGD.A EEL....AAL GEMGPFIPGD
BF1 BR 93B
            RRIDW....L VKRIKERAED SGNESGGD.T EEL....ETM VDMGHLRLLD
C BR 92BR0
C BW 96BW0
            RKIDW....L VKRIRERAED SGNESDGD.T EEL....STM VDMGHLRLLD
C_BW_96BW1
            RKIDW....L IERIRERAED SGNESDGD.H EEL....STM VDMGHLRLLD
C_BW_96BW1
            RRIDR....L VERIREREED SGNESEGD.I EEL....STM VDMGHLRLLD
C BW 96BWl
            KNIDW....L IKRIRERAED SGNESEGD.T EEL....ATM VDMGHLRLLD
C ET ETH22
            RRIDR....L IKRTRERAED SGNESDGD.T EEL....STM VDMGNLRULD
            SKINW....L IKRIRERAED SGNESEGD.T EEL....STM VDMGRLRLLD
C IN 93IN1
C_IN_93IN9
            RKIDW....L İKRIRERAED SGNESEGD.T EEL....STM VDMGRLRLLD
C_IN_93IN9
            RRIDW....L IKRIRERAED SGNESEGD.T EEL....STM VDMGHLRLLD
C_IN_94IN1
            RKIDW....L IKRIRERAED SGNESEGD.T EEL....STM VDMGRLRLLD
C_IN_95IN2
            RKIDW....L IKRIRERAED SGNESEGD.T EEL....STM VDMGRLRLLD
            RKIDR....L IERIRERAED SGNGSEGD.T NEL....ATL VEVGDFDPWV
CRF01 AE C
CRF01 AE C
            RKIDR....L VQRISERAED SGNESEGD.T EEL....AKL VEMGDFDPWV
CRF01_AE_C
            RKIDR....L IERIRERAED SGNESEGD.T DEL....AKL VEMGDFDPWV
CRF01_AE_T
            RKIDR....L VKRIRERAED SGNESEGD.T DEL....AKL VEMGDFDPWV
CRF01 AE T
            RKIDR....L VKRIRERAED SGNESEGD.T DEL....AKL VEMGDFDPWV
            RKIDR....L VKRIREREED SGNESEGD.T DKL....AKL VEMGDFDPWV
CRF01 AE T
            RKIDR....L VKRIRERAED SGNESEGD.T DEL....AQL VEMEDFDPWV
CRF01 AE T
            RKIDR....L VKRIRERAED SGNESEGD.T DEL....AKL VEMGDFDPWV
CRF01 AE T
CRF01 AE T
            RKIDR....L IKRIGERAED SGNESEGD.T DEL....AKL VEMGDFDPWV
            KKIDK....L LDRIRERAED SGNESDGD.A EEL....STL MEMGYD.HIL
CRF02_AG_F
            KKIDK....L LDRIRERAED SGNESDGD.T EEL....STL LEMGYD.NIL
CRF02_AG_F
            KKIDK....L LDRIREREED SGNESEGD.A EEL....SKL MEMGHD.FWI
CRF02 AG G
CRF02 AG N
            KKIDR....L LDRIRERAED SGNESDGD.T EEL....STL MEMGYE.YIL
CRF02 AG S
            KKIDR....L LDRIRERAED SGNESDGD.T EEL....STL MEMGYD.NIL
CRF02 AG S
            GKIDK....L LDRIRERAED SGNESDGD.T EEL....STL LEMGYDNAAL
CRF03 AB R
           RKIDR....L IDRIRERAED SGNESEGD.Q E.....AL MEMGHLVPWD
CRF03 AB R
           RKIDR....L IDRIRERAED SGNESEGD.Q E.....AL MEMGHLAPWD
CRF04_cpx_
            RRIDS....L YNRIRERAED SGNESDGD.A EEL....STL VGMGNFDPWV
CRF04_cpx_
            RKIDR....L YKRIRERAED SGNESDGD.T EEL....STL VGMGDFDPWV
CRF04_cpx
            RKIDR....L CKRIIERAED SGNDSDGD.T EEL....STL VDMGDFHPLV
           RKINR....L YKRIRERAED SGNESEGD.A EEL....AAL GEVGPFIPGD
CRF05_DF_B
           RKINR....L YKRIRERAED SGNESEGD.A EEL....AAL GEMGPFIPGN
CRF05 DF B
            KKIEK....L LDRIRERAED SGNESEGD.T DEL....ATL MEMGDFDPWV
CRF06_cpx
CRF06 cpx
            RKIEK....L LNRIRERAED SGNESEGD.T EEL....AAF MEMGNFDPWV
CRF06_cpx_
            KKIEK....L LDRIRERAED SGNESEGD.T DEL....ATL MEMGNFDPWV
CRF06_cpx_
            KKIEK....L LDRIREREED SGNDSEGD.T EEL....ATL MEMGNFDPWV
CRF11_cpx_
           KKIDR....L IDRIRERAED SGNESEGD.T EEL....ARL VEMGPHDQWN
CRF11_cpx
           R.....K DRLRIRRAED SGNESEGD.T EEL....AQL VEMGPHDLWN
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RKIDW....L IDRIREREED SGNESEGDKE ELS....TL. VEMGHHAPWD
D CD 84ZR0
D CD ELI K
            RRIDC....L LDRITERAED SGNESEGDRE KLS....KL. VEMGHHAPWD
D CD NDK M
            RKIDC....L IDRIRERAED SGNESEGERE BLS....KL. VEMGHHAPWD
D UG 94UG1
            RKIDW....L IDRIRERAED SGNESEGDKE BLS....AL. VEMGHDAPWD
F1 BE V185
            RKINK....L YKRIRERAED SGNESEGD.A BEL....AAL GEMGPFIPGD
F1_BR_93BR RKINR....L YKRISERAED SGNESEGD.A BEL....AAL GEVGPFIPGD
F1_F1_FIN9 RKINR....L YIRIRERAED SGNESEGD.A EEL....AAL GKMGPFIPGD
F1_FR_MP41 RKINR....L YERIRERAED SGNESEGD.A EEL....AAL GEMGSFISGD
F2 CM MP25
            KRINR....L YERIIERAED SGNESEGD.A EEL....AAL GEVGPLIPGD
F2KU BE VI
            ERINQ....L YNRLIERAED SGNESEGE.A EEL....AAL GEVGHLVLGN
            KRIEK....L LDRIRERAED SGNESEGD.T BEL....ATL MELGDFDPWV
G_BE_DRCBL
G NG 92NG0
            KKIEK....L LDRIRERAED SGNESEGD.T EEL....ATL MEMGDFDPWV
G SE SE616
            KRIGK....L LDRIRERAED SGNESDGD.T BEL....VTL VEMGDFDPWV
H BE VI991
            RKIDR....L IERIRERAED SGNESDGD.T BEL....SKL VEMGHLNLGY
H BE VI997
            KKIDR....L IQRIIEGAED SGNESD.... EEL....STM VERGHLTFGY
H CF 90CF0
            KKIDR....L IERIGERAED SGNESDGD.T EEL....SKL MEMGHLNLGY
J_SE_SE702
            RKIDK....L INRIRERAED SGNESDGD.T DEL....AEL VEMGPHDLWN
J_SE_SE788
            RKIDK....L IDRIRERAED SGNESDGD.T EEL....ADL VERCPHDLWN
K_CD_EQTB1
            KRINW....L FDRIRERAED SGNESEGD.T EEL....AAL GETGHLILGD
K CM MP535
            KRINW....L IDRIRERAED SGNESEGD.A EEL....ADI GELGHLILGN
N CM YBF30
            EKIKH....I RQRIREREED SGNESDGD.A EWLDGDEEWL VTLLSSSKLD
O CM ANT70
            DRKEREILER LRRIREIRDD SDYESNGE.. EEQ.....EV MDLVLSHGFD
O CM MVP51
            DRREQEILER LRRIKEIRDD SDYESNEE.. EQQ.....EV MELIHSHGFA
O_SN_99SB_
            DKREREILER LRRIRQIEDD SDYESDGT. EEQ.....EV RDLVHSYGFD
O SN 99SE
            DRREREILER LRRIRQIEDD SDYESDGK.. EEQ.....EV RDLVHGYGFD
U CD 83C
            RKIDW....L IDRIRERAED SGNESEGD.T EEL....STL VEMEPDNFRN
            101
00BW0762_1
            ANGL..
00BW0768_2
            GNDL..
00BW0874_2
            VNDL..
00BW1471_2
            VNDL..
            DL....
00BW1616 2
00BW1686 8
            VNVL..
00BW1759 3
            DNNL..
00BW1773 2
            INH...
00BW1783 5 AHDL..
00BW1795 6
           ANNL..
00BW1811_3
            IINY..
00BW1859_5
            INDL..
00BW1880_2
           ANDL..
00BW1921_1
           HGL...
00BW2036 1
            VHDL..
00BW2063 6
           ANDL..
00BW2087 2
           VNDL..
00BW2127 2
           DL...
00BW2276 7
           GNDL..
00BW3819 3
           AHDL..
00BW3842 8
           L....
00BW3871_3
           VNDI..
00BW3876_9
           INNL..
00BW3886_8
           VNNL..
00BW3891_6
           VNDV..
00BW3970_2
           VTDL..
00BW5031_1
           VNDL..
96BW01B21
           DNAL..
 96BW0407
           DI....
 96BW0502
           VNN...
96BW06 J4
           NL...
96BW11_06
           ANDL..
```

```
96BW1210
             ADGL..
 96BW15B03
             L....
 96BW16_26
             INN...
 96BW17A09
             VNDL..
 96BWMO1 5
             TNDL..
 96BWMO3_2
             INL...
98BWMC12_2
             DNEL..
98BWMC13_4
             VNDL..
98BWMC14_a
            VM....
98BWMO14_1
            ANDL..
98BWM018_d
             ANDL..
98BWMO36_a
             AHDL..
98BWM037_d
             ANDL..
99BW3932 1
             . . . . . .
99BW4642 4
             VNDL..
99BW4745_8
            DL...
99BW4754 7
             VNDL..
99BWMC16_8
            ANDL..
A2_CD_97CD
            DNDV..
A2_CY_94CY
A2D___97KR
             VNNV..
             AND...
A2G CD 97C
             GDNL..
A BY 97BL0
             DNNV..
A_KE_Q23_A
             NNIL..
A_SE_SE659
            DNNL..
A SE SE725
            DNDL..
A SE SE753
             GNNL..
A_SE SE853
            DNNL..
A_SE_SE889
            NNNL..
A_SE_UGSE8
            DNNL..
A_UG_92UG0
            DNNL..
A_UG U455
             DNNL..
AC_IN_2130
            VNGL..
AC_RW_92RW
            VNNL..
AC_SE_SE94
             VNNL..
ACD_SE_SE8
            DINL..
ACG BE VII
            AIDL..
AD SE SE69
            VDDM..
AD_SE_SE71
            DNNL..
ADHK NO 97
            VADL..
ADK_CD_MAL
            VDDL..
AG_BE_VI11
AG_NG_92NG
            GDNL..
            GDNL..
AGHU GA VI
            VNDL..
AGU CD Z32
            GDNL..
AJ BW BW21
            VNDL..
B AU VH AF
            VDDL..
B CN RL42
            VDDL..
B DE D31 U
            VDDL..
B_DE_HAN_U
            VNDQ..
B_FR_HXB2_
            VDDL..
B_GA_OYI_M
            VDDM..
B_GB_CAM1_
            VNDL..
B_GB_GB8_A
            VDDL..
B GB MANC
            VDDL..
B_KR_WK_AF
            VDDL..
B_NL_3202A
            VDDL..
B_TW_TWCYS
            VNDQ..
B US BC LO
            IDDL..
B_US_DH123
            IDDL..
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B_US_JRCSF
             INDL..
B US MNCG
             INDL..
B_US_P896
             VDDL..
B US RF M1
             VDDL..
B US SF2 K
             VDDL..
B_US_WEAU1
             IDDL..
B_US_WR27_
             VDDL..
B_US_YU2_M
             VDDL..
BF1_BR_93B
             IDNL..
C BR 92BR0
             GNDL . .
C_BW_96BW0
             DN . . . .
C_BW_96BW1
             ANDL..
C_BW_96BW1
             ADGL..
C BW 96BW1
             L....
C ET ETH22
             VNDL..
C IN 93IN1
             VNDL..
C_IN_93IN9
             VNDL..
C_IN_93IN9
             VNDM..
C_IN_94IN1
             VNDL..
C_IN_95IN2
CRF01_AE_C
             VNDL..
             GDNL..
CRF01_AE_C
             GDNL..
CRF01_AE_C
             GDNV..
CRF01 AE T
             GDNL..
CRF01 AE T
            GDNL..
CRF01 AE T
            GDNV..
CRF01 AE T
            GDNL..
CRF01_AE_T
            GDNL..
CRF01_AE_T
            GDNL..
CRF02_AG_F
CRF02_AG_F
CRF02_AG_G
             DNDNL.
             DNDNL.
             DNL...
CRF02 AG N
            DNDNL.
CRF02 AG S
            DNDNL.
CRF02 AG S
            DIDNL.
CRF03_AB_R
            ADDL..
CRF03 AB R
            ADDL..
CRF04_cpx_
             GDNL..
CRF04_cpx_
            GNNV..
CRF04_cpx_
            GNNL..
CRF05_DF_B
            INNL..
CRF05 DF B
            INNL..
CRF06_cpx_
            GDNL..
CRF06_cpx_
            GDNL..
CRF06_cpx_
            GDNL..
CRF06_cpx_
            GDNL..
CRF11_cpx_
            VNDL..
CRF11 cpx
            VNDL . . ·
D_CD_84ZR0
            VDDDL.
D_CD_ELI_K IDDL..
D_CD_NDK_M
            VDDL..
D_UG_94UG1
            ADDM..
F1_BE_VI85
            INNL..
F1_BR_93BR
            INNL..
F1_FI_FIN9
            VNNL..
F1 FR MP41
            INNL..
F2 CM MP25
            INNL..
F2KU_BE_VI
            IHNL..
G_BE_DRCBL
            GDNL..
G_NG_92NG0
            GNNL..
```

SOMSBORS TREBUT

G_SE	SE616	GDNL
H_BE	VI991	VADL
H_BE	VI997	VADL
H_CF	90CF0	VADL
J_SE	_SE702	VNDL
J_SB	SE788	VNDL
K_CD	EQTB1	INNL
K_CM	MP535	IDNL
N_CM	YBF30	QGNWV.
O_CM	ANT70	NPMFEP
O_CM	MVP51	NPMFEL
O_SN	99SE_	NPMFEL
O_SN	99SE_	NPMFEP
II CD	920	DMDM

Table 20. BLASTP Sequences producing significant alignments with S20757 (HBV Polymerase subtype ayw)

		Score	E:
•		(bits)	Value
gi 93080 pir S20757 DNA-directed DNA polymerase (E			
gi 8925755 gb AAF81607.1 DNA polymerase/reverse tr	ancorint	1553	0.0
gi 1514497 emb CAA68864.1 P [Hepatitis B virus]	anscript	1489	0.0 ã.o
gi 27466573 gb AA012632.1 polymerase [Hepatitis B	viruel	1488	0.0
91 525/489 gb AAD41360.1 polymerase [Hepatitis B v	virus)	1482 1482	0.0 0.0
gili18876 sp P03156 DPOL HPBVY P protein [Includes:	DNA-dir	1482	0.0
91 27466565 gD AAO12625.1 polymerase [Hepatitis B	virusl	1481	0.0
gile 7003 pir JDVLVB DNA-directed DNA polymerase (E	C 2.7.7	1480	0.0
91 59433 emb CAA46352.1 polymerase ORF [Hepatitis	B virusl	1480	0.0
g1 6692498 gb AAF24666.1 polymerase [Hepatitis B v	irus]	1479	0.0
g1 6692505 gb AAF24673.1 polymerase [Hepatitis B v	irusl	1479	0.0
gi 2117935 pir S71785 DNA-directed DNA polymerase	(EC 2.7	1477	0.0
gi[28436101[db]]BAC5/445.1 polymerase [Hepatitis B	virusl	1476	0.0
- The purpose of	EC 2.7.7	1475	0.0
The same temperature of	virus]	1474	0.0
, ,	virus]	1474	0.0
	virus]	1473	0.0
	irus]	1472	0.0
	virus	1471	0.0
gi 18621125 emb CAC87015.1 polymerase [Hepatitis B gi 1359679 emb CAA66424.1 polymerase [Hepatitis B	virus	1471	0.0
gi 6692492 gb AAF24660.1 polymerase [Hepatitis B v	virusj	1470	0.0
gi 2182121 gb AAB59972.1 DNA polymerase [Hepatitis	Trusi	1468	0.0
gi 4140295 emb CAA10539.1 polymerase [Hepatitis B.	Aimaj P Aiinsi	1467	0.0
gi 28436096 dbj BAC57441.1 polymerase [Hepatitis B	virusi	1467	0.0
gi 2829156 gb AAC40810.1 polymerase [Hepatitis B v	imel	1466 1464	0.0
91/2/466519/9b/AAO12604.1/ polymerase (Hepatitis B.	virusl >	1463	0.0 0.0
91 110009 SP P24024 DPOL HPBVA P protein [Includes:	DNA-dir	1462	0.0
gi 2/466525 gb AAO12672.1 polymerase [Hepatitis B	virusl	1461	0.0
91 762933 [emb CAA59514.1] polymerase [Hepatitis B v	irusl	1461	0.0
gi 22135690 gb AAM09033.1 polymerase [Hepatitis B	virus]	1459	0.0
gi Olimerase/reverse to	ranscrip	1455	0.0
gi 6063465 dbj BAA85373.1 DNA polymerase/reverse tr gi 27466605 gb AA012660.1 polymerase [Hepatitis B.	ranscrip	1454	0.0
T 3 TELEPHOLOGICAL D	virus]	1451	0.0
The state of the particle of t	irus]	1451	0.0
	rus]	1450	0.0
gi 313784 emb CAA42466.1 polymerase [Hepatitis B v: gi 27466597 gb AA012653.1 polymerase [Hepatitis B v: gi 15410022 gb 27466597	irus	1446	0.0
gi 15419833 gb AAK97182.1 AF297620_3 polymerase [Hep	virusj	1444	0.0
gi 93082 pir S20752 DNA-directed DNA polymerase (EG	patitis	1442	0.0
91/2/400013/90/AAU12667.1/ polymerase [Henatitie p ,	- 4././ virual	1441 1435	0.0
gi 27466589 gb AA012646.1 polymerase [Hepatitis B]	viruel		0.0
gi 27466538 gb AA012618.1 polymerase [Henaritis B]	virusj	1434	0.0
gi 27466581 gb AA012639.1 polymerase [Henatitis B ;	virus)	1432 1431	0.0 0.0
91 15419828 9D AAK97178.1 AF297619 3 polymerase (Her	patitis	1429	0.0
gi 27466544 gb AA012681.1 polymerase [Hepatitis B	virusl	1427	0.0
91 27466557 gb AA012692.1 polymerase [Hepatitis B v	virusl	1423	0.0
91 10 / 51312 9D AAL 25951.1 polymerase protein (Henat	citis B	1382	0.0
91 119350 /3 [9D AAG41955.1 AF305327 2 nolymerage [uer	oatitis	1379	0.0
gi 13491150 gb AAK27856.1 AF330110_3 polymerase [Her	patitis	1368	0.0
gilo116700 db] BAA32859.2 pol protein (Hepatitis B	virusl	1368	0.0
91 3551332 db] BAA32886.1 pol protein [Hepatitis B	virusl	1368	0.0
91 28812222 db] BAC65108.1 polymerase protein [Hepa	atitis B	1368	0.0
91 0091303 GD] BAA89330.1 polymerase protein [Hepat	citis B	1368	0.0
gi 118872 sp P12900 DPOL_HPBVL P protein [Includes:	DNA-dir	1368	0.0

```
gi | 560084 | dbj | BAA04927.1 |
                             DNA polymerase [Hepatitis B virus]
                                                                      1367
 gi|560089|dbj|BAA04931.1|
                             DNA polymerase [Hepatitis B virus]
                                                                      1367
                                                                              0.0
gi | 6116731 | dbj | BAA32957.2 |
                              pol protein [Hepatitis B virus]
                                                                      1366
                                                                              0.0
qi | 6691495 | dbj | BAA89322.1 |
                              polymerase protein [Hepatitis B ...
                                                                      1365
gi|7188655|gb|AAF37833.1|AF222323_2 polymerase [Hepatitis B...
                                                                              0.0
                                                                              0.0
gi|6063460|dbj|BAA85369.1| DNA polymerase/reverse transcrip...
                                                                      1364
                                                                              0.0
 gi|3551347|dbj|BAA32898.1|
                              pol protein [Hepatitis B virus]
                                                                      1364
                                                                              0.0
gi 6691500 dbj BAA89326.1 polymerase protein [Hepatitis B ...
                                                                      1363
                                                                              0.0
gi|28812217|dbj|BAC65104.1| polymerase protein [Hepatitis B...
                                                                      1363
                                                                             .0.0
gi 3551342 dbj BAA32894.1 pol protein [Hepatitis B virus]
                                                                      1363
                                                                              0.0
gi|628080|pir||S43491 DNA-directed DNA polymerase (EC 2.7.7...
                                                                      1363
                                                                              0.0
gi|12246972|gb|AAG49670.1|AF223956_3 polymerase [Hepatitis ...
                                                                      1362
                                                                              0.0
gi|3551293|dbj|BAA32852.1| pol protein [Hepatitis B virus]
                                                                      1362
                                                                              0.0
gi|12246964|gb|AAG49663.1|AF223955_3 polymerase [Hepatitis ...
                                                                      1362
gi|21624231|dbj|BAC01103.1| polymerase protein [Hepatitis B...
                                                                              0.0
                                                                              0.0
gi|118874|sp|P03157|DPOL_HPBVR P protein [Includes: DNA-dir...
                                                                              0.0
gi|6009784|dbj|BAA85065.1| polymerase [Hepatitis B virus]
                                                                      1361
gi|22651880|gb|AAN03491.1|AF286594_3 DNA polymerase {Hepati...
                                                                      1360
                                                                              0.0
gi | 18252591 | gb | AAL66348.1 | AF461043 2 P protein [Hepatitis B...
                                                                      1360
                                                                              0.0
gi|15778326|gb|AAL07381.1|AF411409_4 polymerase [Hepatitis ...
                                                                      1360
                                                                              0.0
gi 3551268 dbj BAA32832.1 pol protein [Hepatitis B virus]
                                                                      1360
                                                                              0.0
gi|14290241|gb|AAK59316.1|AF384371_2 polymerase [Hepatitis ...
                                                                      1358
gi |6063435 |dbj |BAA85353.1 | DNA polymerase/reverse transcrip...
                                                                              0.0
                                                                      1358
                                                                              0.0
gi | 6063440 | dbj | BAA85357.1 |
                             DNA polymerase/reverse transcrip...
                                                                      1358
gi|3551283|dbj|BAA32844.1| pol protein [Hepatitis B virus]
                                                                              0.0
                                                                      1358
                                                                              0.0
gi|18252536|gb|AAL66307.1|AF458664_3 polymerase [Hepatitis ...
                                                                      1358
                                                                              0.0
gi|6009769|dbj|BAA85053.1| polymerase [Hepatitis B virus]
                                                                      1358
gi|13991865|gb|AAK51533.1|AF363961_2 polymerase [Hepatitis ...
                                                                      1357
                                                                              0.0
gi|6063425|dbj|BAA85382.1| DNA polymerase/reverse transcrip...
                                                                      1357
                                                                             0.0
gi|2626986|dbj|BAA23435.1| DNA polymerase [Hepatitis B viru...
                                                                      1357
                                                                              0.0
gi 4490402 emb CAB38767.1 P protein [Hepatitis B virus]
                                                                      1357
                                                                              0.0
gi|22415735|gb|AAM95242.1| DNA polymerase/reverse transcrip...
                                                                      1357
                                                                              0.0
gi|10934057|dbj|BAB16885.1| polymerase [Hepatitis B virus]
                                                                      1356
                                                                             0.0
gi|18252556|gb|AAL66323.1|AF461359_3 polymerase [Hepatitis ...
                                                                      1356
                                                                             0.0
gi|2627009|dbj|BAA23455.1| DNA polymerase [Hepatitis B virus]
gi|560074|dbj|BAA04919.1| DNA polymerase [Hepatitis B virus]
                                                                      1356
                                                                             0.0
                                                                      1356
                                                                             0.0
gi|479847|pir||S35527 DNA-directed DNA polymerase (EC 2.7.7...
                                                                             0.0
gi | 18252545 | gb | AAL66314.1 | AF461357_2 polymerase [Hepatitis ...
                                                                      1356
gi | 1742906 | dbj | BAA09083.1 | DNA polymerase [Hepatitis B virus]
                                                                      1355
                                                                             0.0
gi 6009764 dbj BAA85049.1 polymerase [Hepatitis B virus] >...
                                                                      1355
                                                                             0.0
gi|2627002|dbj|BAA23449.1| DNA polymerase [Hepatitis B virus]
                                                                      1355
                                                                             0.0
gi 6063455 dbj BAA85365.1 DNA polymerase/reverse transcrip...
                                                                      1355
                                                                             0.0
gi|10441115|gb|AAG16953.1|AF182804_4 polymerase [Hepatitis ...
                                                                      1354
                                                                             0.0
gi|6009774|dbj|BAA85057.1| polymerase [Hepatitis B virus]
                                                                      1353
                                                                             0.0
gi|4490407|emb|CAB38771.1|
                              P protein [Hepatitis B virus]
                                                                      1353
                                                                             0.0
gi | 3582359 | dbj | BAA32913.1 |
                              pol protein [Hepatitis B virus]
                                                                      1353
                                                                             0.0
gi|3582355|dbj|BAA32874.1|
                             pol protein [Hepatitis B virus]
                                                                             0.0
gi|12246980|gb|AAG49677.1|AF223957_3 polymerase [Hepatitis ...
                                                                      1352
gi|16751307|gb|AAL25947.1| polymerase protein [Hepatitis B ...
                                                                      1352
                                                                             0.0
gi 3582375 dbj BAA32925.1 pol protein [Hepatitis B virus]
                                                                      1352
gi|15778340|gb|AAL07392.1|AF411412_4 polymerase [Hepatitis ...
                                                                             0.0
                                                                      1352
                                                                             0.0
gi|4206637|gb|AAD11755.1| DNA polymerase [Hepatitis B virus]
                                                                      1352
                                                                             0.0
gi|15425690|dbj|BAB64319.1| polymerase [Hepatitis B virus]
                                                                      1352
                                                                             0.0
gi|3551352|dbj|BAA32902.1| pol protein [Hepatitis B virus]
gi|3582395|dbj|BAA32963.1| pol protein [Hepatitis B virus]
                                                                      1352
                                                                             0.0
                                                                      1352
                                                                             0.0
gi|5114071|gb|AAD40205.1|AF090839_2 polymerase [Hepatitis B...
                                                                      1352
                                                                             0.0
gi|9082085|gb|AAF82723.1|AF233236_2 pol [Hepatitis B virus]
gi|6983935|gb|AAF34734.1|AF160501_2 polymerase [Hepatitis B...
                                                                      1352
                                                                             0.0
                                                                             0.0
gi|560094|dbj|BAA04935.1| DNA polymerase [Hepatitis B virus]
                                                                      1351
                                                                             0.0
gi|18032033|gb|AAL49990.1| polymerase [Hepatitis B virus]
                                                                      1351
                                                                             0.0
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gi|18146671|dbj|BAB82392.1| polymerase [Hepatitis B virus]
                                                                              1351
                                                                                       0.0
gi 6006322 dbj BAA84819.1 polymerase protein [Hepatitis B ...
                                                                              1350
                                                                                       0.0
gi|18252551|gb|AAL66319.1|AF461358_3 polymerase [Hepatitis ...
                                                                              1350
                                                                                       0.0
gi|7188649|gb|AAF37828.1|AF222322_2 polymerase [Hepatitis B...
                                                                              1350
                                                                                       0.0
gi|12060441|dbj|BAB20611.1| DNA polymerase [Hepatitis B virus]
                                                                              1350
                                                                                       0.0
gi|18845085|gb|AAL79545.1|AF473543_4 P protein [Hepatitis B...
                                                                              1350
                                                                                       0.0
gi|3551322|dbj|BAA32878.1| pol protein [Hepatitis B virus]
                                                                              1350
gi|12246956|gb|AAG49656.1|AF223954_4 polymerase [Hepatitis ...
                                                                              1350
                                                                                       0.0
gi 6063430 dbj BAA85349.1 DNA polymerase/reverse transcrip...
                                                                              1350
                                                                                       0.0
gi|2288872|dbj|BAA21665.1| DNA polymerase [Hepatitis B virus]
gi|1220111|dbj|BAA04072.1| DNA polymerase [Hepatitis B virus]
                                                                                       0.0
                                                                                       0.0
gi|9454168|gb|AAF87689.1| polymerase protein [Hepatitis B v...
                                                                              1349
                                                                                       0.0
gi | 18146683 | dbj | BAB82402.1 | polymerase [Hepatitis B virus]
                                                                              1349
                                                                                       0.0
gi|3551278|dbj|BAA32840.1| pol protein [Hepatitis B virus] gi|3551372|dbj|BAA32939.1| pol protein [Hepatitis B virus]
                                                                              1349
                                                                                       0.0
                                                                              1349
                                                                                       0.0
gi|19849035|gb|AAL99437.1|AF405706_3 polymerase [Hepatitis ...
                                                                              1349
                                                                                       0.0
gi|3551357|dbj|BAA32906.1| pol protein [Hepatitis B virus]
                                                                              1349
                                                                                       0.0
gi | 15778321 | gb | AAL07377.1 | AF411408_4 polymerase [Hepatițis ...
                                                                              1348
                                                                                       0.0
gi|15072542|gb|AAK81690.1| polymerase protein [Hepatitis B ... gi|21624238|dbj|BAC01109.1| polymerase protein [Hepatitis B...
                                                                              1348
                                                                                       0.0
                                                                              1348
                                                                                       0.0
gi|12247012|gb|AAG49705.1|AF223961_3 polymerase [Hepatitis ...
                                                                                       0.0
gi 5114086 gb AAD40217.1 AF090842_2 polymerase [Hepatitis B...
                                                                                       0.0
gi|3582407|dbj|BAA32972.1| pol protein [Hepatitis B virus]
gi|15425698|dbj|BAB64325.1| polymerase [Hepatitis B virus]
                                                                              1347
                                                                                       0.0
                                                                              1347
                                                                                       0.0
gi|18146665|dbj|BAB82387.1| polymerase [Hepatitis B virus]
                                                                              1347
                                                                                       0.0
gi|23194252|gb|AAN15074.1| P protein [Hepatitis B virus]
                                                                              1347
                                                                                       0.0
gi|560079|dbj|BAA04923.1| DNA polymerase [Hepatitis B virus]
                                                                              1347
                                                                                       0.0
gi|10443833|gb|AAG17595.1|AF241410_3 polymerase [Hepatitis ...
                                                                              1346
                                                                                       0.0
gi|13991870|gb|AAK51537.1|AF363962_2 polymerase [Hepatitis ...
                                                                              1346
                                                                                       0.0
gi|4007054|emb|CAA10426.1| DNA polymerase [Hepatitis B virus]
                                                                              1346
                                                                                       0.0
gi|3551362|dbj|BAA32910.1| pol protein [Hepatitis B virus]
                                                                              1346
                                                                                       0.0
gi|18146677|dbj|BAB82397.1| polymerase [Hepatitis B virus]
                                                                                       0.0
gi|12246988|gb|AAG49684.1|AF223958_3 polymerase [Hepatitis ...
                                                                              1346
                                                                                       0.0
gi | 15211897 | emb | CAC51286.1 | polymerase [Hepatitis B virus] gi | 18389989 | gb | AAL68823.1 | polymerase [Hepatitis B virus] gi | 3582363 | dbj | BAA32916.1 | pol protein [Hepatitis B virus]
                                                                              1345
                                                                                       0.0
                                                                              1345
                                                                                       0.0
                                                                              1345
                                                                                       0.0
gi|10441110|gb|AAG16949.1|AF182803_4 polymerase [Hepatitis ... gi|10443841|gb|AAG17602.1|AF241411_3 polymerase [Hepatitis ...
                                                                              1345
                                                                                       0.0
                                                                              1345
                                                                                       0.0
gi|3551382|dbj|BAA32947.1| pol protein [Hepatitis B virus]
                                                                              1345
                                                                                       0.0
gi|3582387|dbj|BAA32950.1| pol protein [Hepatitis B virus]
                                                                              1344
                                                                                       0.0
gi 3551317 dbj BAA32871.1 pol protein [Hepatitis B virus]
                                                                              1344
                                                                                       0.0
gi|10441104|gb|AAG16944.1|AF182802_3 polymerase [Hepatitis ...
                                                                              1343
                                                                                       0.0
gi | 118866 | sp | P03159 | DPOL_HPBV2 P protein [Includes: DNA-dir...
                                                                              1343
                                                                                       0.0
gi|15425694|dbj|BAB64322.1| polymerase [Hepatitis B virus]
gi|4007049|emb|CAA10422.1| DNA polymerase [Hepatitis B virus]
                                                                              1343
                                                                                       0.0
                                                                              1343
                                                                                       0.0
gi|29123239|gb|AA062971.1| pol protein [Hepatitis B virus]
                                                                              1343
                                                                                       0.0
gi 4007064 emb CAA10438.1 DNA polymerase [Hepatitis B virus]
                                                                              1342
                                                                                       0.0
gi|452623|emb|CAA53358.1| polymerase [Hepatitis B virus]
                                                                              1342
                                                                                       0.0
gi | 18252541 | gb | AAL66311.1 | AF458665_3 polymerase [Hepatitis ...
                                                                              1342
                                                                                       0.0
gi|527443|emb|CAA84791.1| DNA polymerase [Hepatitis B virus]
                                                                              1342
                                                                                       0.0
gi|15211890|emb|CAC51280.1| polymerase [Hepatitis B virus]
                                                                              1342
                                                                                       0.0
gi|329617|gb|AAA62812.1| DNA polymerase
                                                                              1341
                                                                                       0.0
gi|4007079|emb|CAA10454.1| DNA polymerase [Hepatitis B virus]
                                                                              1341
                                                                                       0.0
gi | 9454173 | gb | AAF87693.1 | polymerase protein [Hepatitis B v... gi | 452628 | emb | CAA53354.1 | polymerase [Hepatitis B virus] gi | 3582367 | dbj | BAA32919.1 | pol protein [Hepatitis B virus]
                                                                              1341
                                                                                       0.0
                                                                              1341
                                                                                       0.0
                                                                              1340
                                                                                       0.0
gi|5114066|gb|AAD40201.1|AF090838_2 polymerase [Hepatitis B...
                                                                              1340
                                                                                       0.0
gi|15419860|gb|AAK97203.1|AF297625_3 polymerase [Hepatitis ...
                                                                              1340
                                                                                       0.0
gi|4490412|emb|CAB38775.1| P protein [Hepatitis B virus]
                                                                              1340
                                                                                       0.0
gi|18252566|gb|AAL66331.1|AP461361_3 polymerase [Hepatitis ...
                                                                              1340
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gi|4007059|emb|CAA10430.1| DNA polymerase [Hepatitis B virus]
                                                                    1340
gi|5114081|gb|AAD40213.1|AF090841_2 polymerase [Hepatitis B...
                                                                    1339
                                                                            0.0
gi 3582371 dbj BAA32922.1 pol protein [Hepatitis B virus]
                                                                    1339
gi|12247003|gb|AAG49697.1|AF223960_4 polymerase [Hepatitis ...
                                                                            0.0
                                                                    1339
                                                                            0.0
gi|4033548|emb|CAA10450.1| DNA polymerase [Hepatitis B virus]
                                                                    1339
                                                                            0.0
gi|3892581|emb|CAA09962.1| polymerase [Hepatitis B virus]
                                                                    1339
                                                                            0.0
gi|5114076|gb|AAD40209.1|AF090840_2 polymerase [Hepatitis B...
                                                                    1338
gi|12060436|dbj|BAB20607.1| DNA polymerase [Hepatitis B virus]
                                                                           0.0
                                                                    1338
                                                                           0.0
gi | 118868 | sp | P17100 | DPOL_HPBV9 P protein [Includes: DNA-dir...
                                                                    1337
                                                                           0.0
gi|27466434|gb|AA012555.1| polymerase [Hepatitis B virus]
                                                                    1337
                                                                           0.0
gi|3582399|dbj|BAA32966.1| pol protein [Hepatitis B virus]
                                                                    1337
                                                                           0.0
gi|3551273|dbj|BAA32836.1| pol protein [Hepatitis B virus]
                                                                    1337
                                                                           0.0
gi 14285168 gb AAK58873.1 polymerase [synthetic construct]...
                                                                    1337
                                                                           0.0
gi|3582391|dbj|BAA32953.1|
                            pol protein [Hepatitis B virus]
gi|15419845|gb|AAK97191.1|AF297622_3 polymerase [Hepatitis ...
                                                                    1337
                                                                           0.0
                                                                    1337
                                                                           0.0
gi|118870|sp|P17393|DPOL_HPBVI P protein [Includes: DNA-dir...
                                                                    1336
                                                                           0.0
gi|3551377|dbj|BAA32943.1| pol protein [Hepatitis B virus]
                                                                    1336
                                                                           0.0
gi|10443825|gb|AAG17588.1|AF241409_3 polymerase [Hepatitis ...
                                                                    1336
gi|10443817|gb|AAG17581.1|AF241408_3 polymerase [Hepatitis ...
                                                                           0.0
                                                                    1336
                                                                           0.0
gi 29124889 gb AA063519.1 pol protein [Hepatitis B virus]
                                                                    1335
                                                                           0.0
gi|399401|sp|P31870|DPOL_HPBVM P protein [Includes: DNA-dir...
                                                                    1335
                                                                           0.0
gi | 6063445 | dbj | BAA85339.1 | DNA polymerase/reverse transcrip...
                                                                    1335
                                                                           0.0
gi | 19568078 | gb | AAL89566.1 |
                             polymerase [Hepatitis B virus]
                                                                    1334
                                                                           0.0
gi|27466426|gb|AA012548.1|
                             polymerase [Hepatitis B virus]
                                                                    1334
                                                                           0.0
gi|22655601|gb|AAN04128.1|
                            polymerase [Hepatitis B virus]
                                                                    1334
                                                                           0.0
gi 8161369 gb AAA69721.2 polymerase [Hepatitis B virus]
                                                                    1334
gi|10441120|gb|AAG16957.1|AF182805_4 polymerase [Hepatitis ... gi|10443809|gb|AAG17574.1|AF241407_3 polymerase [Hepatitis ...
                                                                           0.0
                                                                    1334
                                                                           0.0
                                                                    1333
                                                                           0.0
gi|18146689|dbj|BAB82407.1| polymerase [Hepatitis B virus]
                                                                    1333
gi|4007069|emb|CAA10442.1| DNA polymerase [Hepatitis B virus]
                                                                           0.0
                                                                    1333
                                                                           0.0
gi|18031709|gb|AAK57744.1| polymerase [Hepatitis B virus]
                                                                    1333
                                                                           0.0
gi|18252561|gb|AAL66327.1|AF461360_3 polymerase [Hepatitis ...
                                                                    1332
                                                                           0.0
gi|6959503|gb|AAF33121.1| polymerase protein [orangutan hep...
                                                                    1332
                                                                           0.0
gi|26224721|gb|AAN76318.1|
                             polymerase [Hepatitis B virus]
                                                                    1332
                                                                           0.0
gi|4007074|emb|CAA10446.1|
                             DNA polymerase [Hepatitis B virus]
gi|18031714|gb|AAK57745.1| polymerase [Hepatitis B virus]
                                                                    1332
                                                                           0.0
                                                                           0.0
gi|7434791|pir||S67505 DNA-directed DNA polymerase (EC 2.7....
                                                                    1332
                                                                           0.0
gi|15419855|gb|AAK97199.1|AF297624_3 polymerase [Hepatitis ...
                                                                    1332
gi|7434793|pir||T13468 DNA-directed DNA polymerase (EC 2.7....
                                                                    1331
                                                                           0.0
gi|4323205|gb|AAD16257.1| polymerase [Hepatitis B virus]
                                                                    1331
                                                                           0.0
gi|12060194|dbj|BAB20451.1| DNA polymerase [Hepatitis B virus]
                                                                    1331
                                                                           0.0
gi|23194347|gb|AAN15122.1| polymerase [Hepatitis B virus]
                                                                    1330
                                                                           0.0
gi | 20151228 | gb | AAM12945.1 |
                            DNA polymerase/reverse transcrip...
                                                                    1330
                                                                           0.0
gi|23884547|gb|AAN40009.1| pol protein [Hepatitis B virus]
gi|21431681|gb|AAM53414.1|U87747_3 DNA polymerase/reverse t...
                                                                    1330
                                                                           0.0
gi|3551337|dbj|BAA32890.1| pol protein [Hepatitis B virus]
                                                                    1330
                                                                           0.0
                                                                    1329
                                                                           0.0
gi|5019933|gb|AAD37919.1| P protein [Hepatitis B virus]
                                                                    1329
                                                                           0.0
gi|15419840|gb|AAK97187.1|AF297621_3 polymerase [Hepatitis ...
                                                                    1329
                                                                           0.0
gi|6006331|dbj|BAA84825.1| polymerase protein [Hepatitis B ...
                                                                    1329
                                                                           0.0
gi | 19568073 | gb | AAL89569.1 | polymerase [Hepatitis B virus]
                                                                    1329
                                                                           0.0
gi|29124918|gb|AA063539.1| pol protein [Hepatitis B virus]
                                                                    1328
                                                                           0.0
gi|329630|gb|AAA45483.1| P protein [Hepatitis B virus]
                                                                    1328
                                                                           0.0
gi|15778331|gb|AAL07385.1|AF411410_4 polymerase [Hepatitis ...
                                                                    1328
                                                                           0.0
gi|6566410|dbj|BAA88275.1| P protein [Hepatitis B virus]
                                                                    1328
                                                                           0.0
gi|4490397|emb|CAB38763.1| P protein [Hepatitis B virus]
                                                                    1328
gi|12060187|dbj|BAB20445.1| DNA polymerase [Hepatitis B virus]
                                                                           0.0
                                                                   1327
                                                                           0.0
gi|6063450|dbj|BAA85343.1| DNA polymerase/reverse transcrip...
                                                                   1327
gi|118877|sp|P03155|DPOL_HPBVZ P protein [Includes: DNA-dir...
                                                                           0.0
                                                                   1327
                                                                           0.0
gi|29124883|gb|AA063514.1| pol protein [Hepatitis B virus]
                                                                   1325
                                                                           0.0
gi 4033543 emb CAA10434.1 DNA polymerase [Hepatitis B virus]
                                                                   1325
                                                                           0.0
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gi | 6692525 | gb | AAF24693.1 |
                             polymerase [Hepatitis B virus]
                                                                     1325
gi | 6692559 | gb | AAF24727.1 |
                             polymerase [Hepatitis B virus]
                                                                     1325
                                                                             0.0
gi | 23194340 | gb | AAN15116.1 |
                              polymerase [Hepatitis B virus]
                                                                     1325
                                                                             0.0
gi | 560064 | dbj | BAA04911.1 |
                             DNA polymerase [Hepatitis B virus]
                                                                     1324
                                                                             0.0
gi | 29124898 | gb | AA063526.1 |
                              pol protein [Hepatitis B virus]
                                                                     1324
                                                                             0.0
gi | 29124927 | gb | AA063545.1 |
                              pol protein [Hepatitis B virus]
                                                                     1323
                                                                             0.0
gi | 6692566 | gb | AAF24734.1 |
                             polymerase [Hepatitis B virus]
                                                                     1323
                                                                             0.0
gi|6692553|gb|AAF24721.1|
                             polymerase [Hepatitis B virus]
                                                                     .1323
                                                                             0.0
gi|6692518|gb|AAF24686.1|
                             polymerase [Hepatitis B virus] >g...
                                                                     1323
                                                                             0.0
gi | 1359702 | emb | CAA66444.1 |
                              polymerase [Hepatitis B virus] >...
                                                                     1323
                                                                             0.0
gi|29124867|gb|AA063501.1|
                              pol protein [Hepatitis B virus]
                                                                     1323
                                                                             0.0
gi | 29124872 | gb | AA063505.1 |
                              pol protein [Hepatitis B virus] ...
                                                                     1323
                                                                            0.0
gi|27466479|gb|AA012576.1|
                             polymerase [Hepatitis B virus]
                                                                     1322
                                                                            0.0
gi|6692546|gb|AAF24714.1|
                            polymerase [Hepatitis B virus]
                                                                     1322
                                                                             0.0
gi | 3551312 | dbj | BAA32867.1 |
                             pol protein [Hepatitis B virus]
                                                                     1322
                                                                             0.0
gi|27466487|gb|AA012611.1|
                             polymerase [Hepatitis B virus]
                                                                     1322
                                                                             0.0
gi|118871|sp|P17394|DPOL_HPBVJ P protein [Includes: DNA-dir...
                                                                     1321
0.0
                                                                     1321
                                                                            0.0
gi|19224214|gb|AAL86445.1|AF479684_3 P gene product [Hepati...
                                                                     1321
                                                                            0.0
gi|6692572|gb|AAF24740.1| polymerase [Hepatitis B virus]
                                                                     1321
                                                                            0.0
gi|3551297|dbj|BAA32855.1|
                             pol protein [Hepatitis B virus]
                                                                     1321
                                                                             0.0
gi | 3551327 | dbj | BAA32882.1 |
                             pol protein [Hepatitis B virus]
                                                                     1320
                                                                            0.0
gi | 1359695 | emb | CAA66434.1 |
                              polymerase [Hepatitis B virus]
                                                                     1320
                                                                            0.0
gi | 3551367 | dbj | BAA32932.1 |
                              pol protein [Hepatitis B virus]
                                                                     1320
                                                                            0.0
gi|118873|sp|P17395|DPOL_HPBVO P protein [Includes: DNA-dir...
                                                                     1319
                                                                            0.0
gi|29124862|gb|AA063497.1|
                              pol protein [Hepatitis B virus]
                                                                     1319
                                                                            0.0
gi | 18621110 | emb | CAC87028.1 |
                              polymerase [Hepatitis B virus]
                                                                     1319
                                                                            0.0
gi | 3582403 | dbj | BAA32969.1 |
                              pol protein [Hepatitis B virus]
                                                                     1318
                                                                            0.0
gi | 27261550 | gb | AAN85925.1 |
                              DNA polymerase [Hepatitis B viru...
                                                                     1318
                                                                            0.0
gi|1914703|emb|CAA66699.1|
                             polymerase [Hepatitis B virus]
                                                                     1318
                                                                            0.0
gi|4323200|gb|AAD16253.1|
                            polymerase [Hepatitis B virus]
                                                                     1318
                                                                            0.0
gi|6573293|dbj|BAA88291.1|
                             P protein [Hepatitis B virus]
                                                                     1318
                                                                            0.0
gi | 6006341 | dbj | BAA84833.1 |
                              polymerase protein [Hepatitis B ...
                                                                     1316
                                                                            0.0
gi|6566440|dbj|BAA88286.1|
                              P protein [Hepatitis B virus]
                                                                     1315
                                                                            0.0
gi | 560059 | dbj | BAA04907.1 |
                            DNA polymerase [Hepatitis B virus]
                                                                     1315
                                                                            0.0
gi | 14334410 | gb | AAK59391.1 |
                            polymerase [Hepatitis B virus]
                                                                     1315
                                                                            0.0
gi|5019954|gb|AAD37936.1|
                            P protein [Hepatitis B virus]
                                                                     1315
                                                                            0.0
gi|16117323|dbj|BAB69785.1| polymerase [Hepatitis B virus]
                                                                     1315
gi|7434792|pir||T13473 DNA-directed DNA polymerase (EC 2.7....
                                                                     1315
                                                                            0.0
gi|5019965|gb|AAD37945.1| P protein [Hepatitis B virus]
                                                                     1314
                                                                            0.0
gi|29124908|gb|AA063533.1| pol protein [Hepatitis B virus]
                                                                     1314
                                                                            0.0
gi|6566428|dbj|BAA88281.1|
                            P protein [Hepatitis B virus]
                                                                     1313
                                                                            0.0
gi | 29124894 | gb | AA063523.1 |
                             pol protein [Hepatitis B virus]
                                                                     1311
                                                                            0.0
gi|22135730|gb|AAM09065.1|
                            polymerase [Hepatitis B virus]
                                                                     1311
                                                                            0.0
gi|560069|dbj|BAA04915.1|
                           DNA polymerase [Hepatitis B virus]
                                                                     1311
                                                                            0.0
gi|15419850|gb|AAK97195.1|AF297623_3 polymerase [Hepatitis ...
                                                                     1311
                                                                            0.0
gi|9634217|ref|NP_037757.1|
                              polymerase protein [orangutan h...
                                                                            0.0
gi | 16117333 | dbj | BAB69793.1 |
                              polymerase [Hepatitis B virus]
                                                                     1309
                                                                            0.0
gi | 9971630 | dbj | BAB12582.1 |
                             polymerase protein [Hepatitis B ...
                                                                     1308
                                                                            0.0
gi|27466450|gb|AA012569.1| polymerase [Hepatitis B virus]
                                                                     1306
                                                                            0.0
gi|12247036|gb|AAG49726.1|AF223964_3 polymerase [Hepatitis ...
                                                                     1306
                                                                            0.0
gi|12247028|gb|AAG49719.1|AF223963_3 polymerase [Hepatitis ...
                                                                     1305
                                                                            0.0
gi|5019945|gb|AAD37929.1| P protein [Hepatitis B virus]
                                                                     1305
                                                                            0.0
gi|18146701|dbj|BAB82417.1| polymerase [Hepatitis B virus]
                                                                     1305
                                                                            0.0
gi|12247020|gb|AAG49712.1|AF223962_3 polymerase [Hepatitis ...
                                                                     1304
                                                                            0.0
gi|5019981|gb|AAD37958.1| P protein [Hepatitis B virus]
                                                                     1304
                                                                            0.0
gi|3892582|emb|CAA53343.1|
                            polymerase (Hepatitis B virus)
                                                                     1304
                                                                            0.0
gi | 27466442 | gb | AAO12562.1 |
                             polymerase [Hepatitis B virus]
                                                                     1304
                                                                            0.0
gi | 22135715 | gb | AAM09053.1 |
                             polymerase [Hepatitis B virus]
                                                                     1301
                                                                            0.0
gi|12247044|gb|AAG49733.1|AF223965_3 polymerase [Hepatitis ...
                                                                     1301
                                                                            0.0
```

```
gi|22135725|gb|AAM09061.1|
                              polymerase [Hepatitis B virus]
                                                                      1301
                                                                             0.0
gi|11191880|dbj|BAB17962.1|
                               polymerase [Hepatitis B virus]
                                                                      1300
                                                                             0.0
gi | 3551392 | dbj | BAA32961.1 |
                              pol protein [Hepatitis B virus]
                                                                      1300
                                                                             0.0
gi|6006336|dbj|BAA84829.1|
                              polymerase protein [Hepatitis B ...
                                                                      1299
                                                                             0.0
gi | 2627021 | dbj | BAA23467.1 |
                              DNA polymerase [Hepatitis B virus]
                                                                      1298
                                                                             0.0
gi | 2627015 | dbj | BAA23461.1 |
                              DNA polymerase [Hepatitis B virus]
                                                                      1297
                                                                             0.0
gi|16117328|dbj|BAB69789.1|
                               polymerase [Hepatitis B virus]
                                                                      1297
                                                                             0.0
gi|22135735|gb|AAM09069.1|
                              polymerase [Hepatitis B virus]
                                                                      1297
                                                                             0.0
gi|14485226|gb|AAK62976.1|AF384372_2 polymerase [Hepatitis ...
                                                                      1296
                                                                             0.0
gi|3551288|dbj|BAA32848.1|
                              pol protein [Hepatitis B virus]
                                                                      1295
                                                                             0.0
gi|11191960|dbj|BAB18032.1|
                               polymerase [Hepatitis B virus]
                                                                      1294
                                                                             0.0
gi|11191888|dbj|BAB17969.1|
                               polymerase [Hepatitis B virus]
                                                                      1293
                                                                             0.0
gi|11191840|dbj|BAB17927.1|
                               polymerase [Hepatitis B virus] ...
                                                                      1293
                                                                             0.0
gi|11191920|dbj|BAB17997.1|
                               polymerase [Hepatitis B virus]
                                                                      1293
                                                                             0.0
gi|11191904|dbj|BAB17983.1|
                               polymerase [Hepatitis B virus]
                                                                      1291
                                                                             0.0
gi|11191952|dbj|BAB18025.1|
                               polymerase [Hepatitis B virus]
                                                                      1291
gi|1169410|sp|Q05486|DPOL_HPBVT P protein [Includes: DNA-di...
                                                                             0.0
                                                                      1289
                                                                             0.0
gi|22135705|gb|AAM09045.1| polymerase [Hepatitis B virus]
                                                                      1288
gi|452633|emb|CAA53350.1| polymerase [Hepatitis B virus]
                                                                             0.0
                                                                      1288
gi|18146695|dbj|BAB82412.1| polymerase [Hepatitis B virus]
                                                                             0.0
                                                                     1287
gi|22135710|gb|AAM09049.1| polymerase [Hepatitis B virus]
                                                                             0.0
                                                                     1287
                                                                             0.0
gi|11191864|dbj|BAB17948.1|
                               polymerase [Hepatitis B virus]
                                                                     1286
gi|59451|emb|CAA48354.1| HBV polymerase [Hepatitis B virus]
                                                                             0.0
                                                                     1286
                                                                             0.0
gi|11191848|dbj|BAB17934.1|
                              polymerase [Hepatitis B virus] ...
                                                                     1286
                                                                             0.0
gi|22135700|gb|AAM09041.1|
                             polymerase [Hepatitis B virus]
                                                                     1285
                                                                             0.0
gi|5019976|gb|AAD37954.1|
                             P protein [Hepatitis B virus]
                                                                     1281
                                                                             0.0
gi|22135720|gb|AAM09057.1| polymerase [Hepatitis B virus]
                                                                     1279
                                                                             0.0
gi|5019939|gb|AAD37924.1| P protein [Hepatitis B virus]
                                                                     1276
                                                                             0.0
gi|1914697|emb|CAA66674.1| polymerase [Hepatitis B virus]
                                                                     1273
                                                                             0.0
gi|1914691|emb|CAA66679.1|
                             polymerase [Hepatitis B virus]
                                                                     1271
                                                                             0.0
gi|5019970|gb|AAD37949.1|
                            P protein [Hepatitis B virus]
                                                                     1263
gi|15425702|dbj|BAB64328.1| polymerase [Hepatitis B virus]
                                                                             0.0
                                                                     1258
                                                                             0.0
gi|29124905|gb|AA063531.1|
                             pol protein [Hepatitis B virus]
                                                                     1253
                                                                            0.0
gi|27466464|gb|AA012704.1|
                             polymerase [Hepatitis B virus]
                                                                     1248
                                                                            0.0
gi|27466471|gb|AA012710.1|
                             polymerase [Hepatitis B virus]
gi|18252571|gb|AAL66335.1|AF461362_3 polymerase [Hepatitis ...
                                                                     1244
                                                                            0.0
gi|27466511|gb|AAO12597.1| polymerase [Hepatitis B virus]
                                                                     1243
                                                                            0.0
                                                                     1239
gi|27466457|gb|AAO12698.1| polymerase [Hepatitis B virus]
                                                                            0.0
                                                                     1238
                                                                            0.0
gi|15211905|emb|CAC51293.1| polymerase [Hepatitis B virus]
gi 399402|sp|Q02314|DPOL_HPBVP P protein [Includes: DNA-dir...
                                                                     1227
                                                                            0.0
                                                                     1224
                                                                            0.0
gi | 1914708 | emb | CAA66684.1 |
                             polymerase [Hepatitis B virus]
                                                                     1220 .
                                                                            0.0
gi|27466503|gb|AA012583.1|
                             polymerase [Hepatitis B virus]
                                                                     1184
gi|118867|sp|P12933|DPOL_HPBV4 P protein [Includes: DNA-dir...
                                                                            0.0
                                                                     1157
                                                                            0.0
gi|4468850|emb|CAB38229.1|
                             polymerase [Hepatitis B virus]
                                                                     1122
                                                                            0.0
gi | 1914719 | emb | CAA66694.1 |
                             polymerase [Hepatitis B virus]
                                                                     1101
                                                                            0.0
gi|9630375|ref|NP_046799.1|
                              polymerase [woolly monkey hepat...
                                                                     1049
                                                                            0.0
gi|1185115|emb|CAA51254.1|
                             DNA polymerase [Hepatitis B virus]
                                                                      922
gi|20800461|gb|AAM28642.1|U87746_4 DNA polymerase/reverse t...
                                                                            0.0
gi|21326585|ref|NP_647604.1| P gene product (AA 304-843); c...
                                                                      910
                                                                            0.0
                                                                      907
                                                                            0.0
gi|4377612|emb|CAA53339.1| polymerase [Hepatitis B virus]
                                                                      904
                                                                            0.0
gi|4377613|emb|CAA53338.1|
                             polymerase [Hepatitis B virus]
                                                                      901
                                                                            0.0
gi|1549226|dbj|BAA04073.1| ORF [Hepatitis B virus]
                                                                      898
gi|9454414|gb|AAF87797.1| polymerase [Hepatitis B virus]
                                                                            0.0
                                                                      895
                                                                            0.0
gi|1550614|dbj|BAA04075.1| ORF [Hepatitis B virus]
                                                                      893
                                                                            0.0
gi|59409|emb|CAA32399.1| DNA polymerase [Hepatitis B virus]
                                                                      879
gi|118894|sp|P03160|DPOL_WHV1 P protein [Includes: DNA-dire...
                                                                            0.0
                                                                      727
                                                                            0.0
gi 9626716 | ref | NP 040994.1 | A protein [Ground squirrel hepa... gi 22256032 | ref | NP 671813.1 | DNA polymerase [Woodchuck hepa...
                                                                      727
                                                                            0.0
gi 15637595 gb AAL04547.1 AF410859 1 polymerase [Woodchuck ...
                                                                      725
                                                                            0.0
                                                                      725
                                                                            0.0
gi|15637587|gb|AAL04543.1|AF410855_1 type II mutant polymer...
                                                                            0.0
```

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gi|118895|sp|P12899|DPOL_WHV59 P protein [Includes: DNA-dir...
                                                                                                                  724
                                                                                                                             0.0
 gi|15637597|gb|AAL04548.1|AF410860_1 polymerase [Woodchuck ...
                                                                                                                  724
                                                                                                                             0.0
gi|15637599|gb|AAL04549.1|AF410861_1 polymerase [Woodchuck ...
gi|15637593|gb|AAL04546.1|AF410858_1 defective polymerase [...
                                                                                                                  722
                                                                                                                             0.0
                                                                                                                  721
                                                                                                                             0.0
 gi|118898|sp|P17396|DPOL_WHV8I P protein [Includes: DNA-dir...
                                                                                                                  721
                                                                                                                             0.0
gi|15637591|gb|AAL04545.1|AF410857_1 type I mutant polymera...
gi|15637589|gb|AAL04544.1|AF410856_1 type IV mutant polymer...
                                                                                                                  721
                                                                                                                             0.0
                                                                                                                  717
                                                                                                                           .0.0
 gi|118897|sp|P06275|DPOL_WHV8 P protein [Includes: DNA-dire...
                                                                                                                  706
                                                                                                                             0.0,
 gi|3582379|dbj|BAA32928.1| pol protein [Hepatitis B virus]
                                                                                                                  692
                                                                                                                             0.0
gi|9885813|gb|AAG01539.1|AF291830_2 polymerase [Hepatitis B...
                                                                                                                  692
                                                                                                                             0.0
 gi|118875|sp|P03158|DPOL_HPBVW DNA polymerase
                                                                                                                  680
                                                                                                                             0.0
gi|9628830|ref|NP_043864.1| polymerase [Arctic ground squir...
                                                                                                                  669
                                                                                                                             0.0
gi 8926931 dbj BAA98025.1 pol protein [Hepatitis B virus]
                                                                                                                  669
gi 8926928 dbj BAA98023.1 pol protein [Hepatitis B virus]
gi 8926925 dbj BAA98021.1 pol protein [Hepatitis B virus]
gi 8926934 dbj BAA98027.1 pol protein [Hepatitis B virus]
                                                                                                                             0.0
                                                                                                                  667
                                                                                                                             0.0
                                                                                                                  667
                                                                                                                             0.0
gi | 13345982 | gb | AAK19538.1 | AF335734_2 | polymerase | Hepatitis ... | gi | 12083172 | gb | AAG48743.1 | AF329861_2 | polymerase | Hepatitis ... | gi | 13345979 | gb | AAK19536.1 | AF335733_2 | polymerase | Hepatitis ... | gi | 12083181 | gb | AAG48749.1 | AF329864_2 | polymerase | Hepatitis ... | gi | 12083178 | gb | AAG48747.1 | AF329863_2 | polymerase | Hepatitis ... | gi | 12083178 | gb | AAG48747.1 | AF329863_2 | polymerase | Hepatitis ... | Hepatitis ... | gi | 12083178 | gb | AAG48747.1 | AF329863_2 | polymerase | Hepatitis ... | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Polymerase | Hepatitis ... | Pol
                                                                                                                  655
                                                                                                                  583 e-166
                                                                                                                  583 e-166
                                                                                                                  583
                                                                                                                          e-166
                                                                                                                  582
                                                                                                                          e-166
                                                                                                                  582
                                                                                                                          e-165
gi|12083163|gb|AAG48737.1|AF329858_1 polymerase [Hepatitis ...
                                                                                                                  581 e-165
gi|12083167|gb|AAG48740.1|AF329859_2 polymerase [Hepatitis ...
                                                                                                                  581 e-165
gi|13345988|gb|AAK19542.1|AF335736_2 polymerase [Hepatitis ... gi|13345985|gb|AAK19540.1|AF335735_2 polymerase [Hepatitis ...
                                                                                                                  580 e-165
                                                                                                                  578 e-164
gi|2982339|gb|AAC06361.1| DNA polymerase [Hepatitis B virus]
                                                                                                                 568 e-161
 gi|336159|gb|AAA46774.1| polymerase protein
                                                                                                                  566 e-161
 gi|118899|sp|P11292|DPOL_WHVW6 P protein [Includes: DNA-dir...
                                                                                                                 560
                                                                                                                          e-159
 gi 225532 prf | 1305266C gene P
                                                                                                                  555
                                                                                                                          e-157
 gi|1107586|emb|CAA56892.1| polymerase [Hepatitis B virus]
                                                                                                                  540
                                                                                                                          e-153
 gi|1107579|emb|CAA56878.1| polymerase [Hepatitis B virus]
                                                                                                                  538
                                                                                                                          e-152
 gi|1185116|emb|CAA51255.1| HBsAg [Hepatitis B virus]
                                                                                                                  465
                                                                                                                          e-130
 gi|59414|emb|CAA32405.1| DNA polymerase [Hepatitis B virus]
                                                                                                                 459 e-129
 gi|21326589|ref|NP_647608.1| P gene product, put.DNA polyme...
                                                                                                                 458 e-128
gi|1321828|emb|CAA96556.1| polymerase [Hepatitis B virus]
gi|5019960|gb|AAD37941.1| P protein [Hepatitis B virus]
gi|329652|gb|AAA69719.1| coat protein [Hepatitis B virus]
gi|329651|gb|AAA69720.1| coat protein [Hepatitis B virus]
                                                                                                                 441 e-123
                                                                                                                 440 e-123
                                                                                                                 433 e-121
                                                                                                                 429 e-120
 gi|27466495|gb|AA012590.1| polymerase [Hepatitis B virus]
                                                                                                                 429 e-120
gi|21218028|dbj|BAB96528.1| large S protein [Hepatitis B vi...
                                                                                                                 413 e-115
gi|1321832|emb|CAA96561.1| polymerase [Hepatitis B virus]
                                                                                                                 410
                                                                                                                         e-114
gi|27450190|gb|AA014552.1|AF460225_1 polymerase [Hepatitis ...
                                                                                                                        e-106
                                                                                                                  385
gi|27450188|gb|AA014551.1|AF460224_1 polymerase [Hepatitis ...
                                                                                                                  384 e-106
gi|27450192|gb|AA014553.1|AF460226_1 polymerase [Hepatitis ...
                                                                                                                  383 e-106
gi|27450198|gb|AA014556.1|AF460229_1 polymerase [Hepatitis ...
                                                                                                                  382 e-105
gi|27450196|gb|AA014555.1|AF460228_1 polymerase [Hepatitis ...
                                                                                                                  382 e-105
gi|27450194|gb|AA014554.1|AF460227_1 polymerase [Hepatitis ...
                                                                                                                  382 e-105
gi|27450200|gb|AA014557.1|AF460230_1 polymerase [Hepatitis ... gi|27450202|gb|AA014558.1|AF460231_1 polymerase [Hepatitis ...
                                                                                                                  375 e-103
                                                                                                                 375 e-103
gi|3328370|gb|AAC26832.1| DNA polymerase [Hepatitis B virus]
                                                                                                                 374 e-103
gi|23380174|gb|AAM83022.1| polymerase [Hepatitis B virus]
                                                                                                                 373
                                                                                                                          e-103
gi|23380081|gb|AAM82960.1| polymerase [Hepatitis B virus]
                                                                                                                 373
                                                                                                                          e-103
gi|23380171|gb|AAM83020.1| polymerase [Hepatitis B virus]
                                                                                                                 372
                                                                                                                          e-102
gi|23380180|gb|AAM83026.1| polymerase [Hepatitis B virus]
                                                                                                                 370 e-102
gi|23380177|gb|AAM83024.1|
                                                polymerase [Hepatitis B virus]
                                                                                                                 369 e-102
gi 23380072 gb AAM82954.1
                                                polymerase [Hepatitis B virus]
                                                                                                                 369 e-101
gi|23380084|gb|AAM82962.1|
                                                polymerase [Hepatitis B virus] >...
                                                                                                                 368 e-101
gi|23380078|gb|AAM82958.1|
                                                polymerase (Hepatitis B virus)
                                                                                                                 368 e-101
gi 23380066 gb AAM82950.1
                                                polymerase [Hepatitis B virus]
                                                                                                                 368 e-101
gi|23380111|gb|AAM82980.1|
                                                polymerase [Hepatitis B virus]
                                                                                                                 368 e-101
```

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gi | 23380063 | gb | AAM82948.1 |
                              polymerase [Hepatitis B virus]
                                                                        367
gi | 23380087 | gb | AAM82964.1 |
                              polymerase [Hepatitis B virus]
                                                                       367
                                                                             e-101
gi | 3335627 | gb | AAD13662.1 |
                             DNA polymerase [Hepatitis B virus]
                                                                       366
                                                                            e-101
gi 23380069 gb AAM82952.1
                              polymerase [Hepatitis B virus]
                                                                       366
                                                                             e-101
gi 23380090 | gb | AAM82966.1 |
                              polymerase [Hepatitis B virus]
                                                                       366
                                                                             e-101
gi 23380060 | gb | AAM82946.1 |
                              polymerase [Hepatitis B virus]
                                                                       366
                                                                             e-101
gi 23380105 | gb | AAM82976.1 |
                              polymerase [Hepatitis B virus]
                                                                       365
                                                                             e-100
gi | 23380132 | gb | AAM82994.1 |
                              polymerase [Hepatitis B virus]
                                                                       365
                                                                             e-100
gi|23380093|gb|AAM82968.1|
                              polymerase [Hepatitis B virus]
                                                                       365
                                                                             e-100
gi | 23380183 | gb | AAM83028.1 |
                              polymerase [Hepatitis B virus] >...
                                                                       365
                                                                             e-100
gi 23380120 gb AAM82986.1
                              polymerase [Hepatitis B virus]
                                                                       365
                                                                             e-100
gi|13991875|gb|AAK51541.1|AF363963_2 truncated polymerase [...
                                                                       365
                                                                             e-100
gi 23380129 gb AAM82992.1
                              polymerase [Hepatitis B virus]
                                                                       363
                                                                             e-100
gi |23380186 | gb | AAM83030.1 |
                              polymerase [Hepatitis B virus]
                                                                       363
                                                                             e-100
gi | 23380168 | gb | AAM83018.1 |
                              polymerase [Hepatitis B virus]
                                                                       363
                                                                             e-100
gi | 23380075 | gb | AAM82956.1 |
                              polymerase [Hepatitis B virus]
                                                                       363
gi 23380123 gb AAM82988.1
                              polymerase [Hepatitis B virus]
                                                                       361
                                                                             3e-99
gi 23380135 | gb | AAM82996.1 |
                              polymerase [Hepatitis B virus]
                                                                       357
                                                                             4e-98
gi | 23380030 | gb | AAM82926.1 |
                              polymerase [Hepatitis B virus]
                                                                       351
                                                                             3e-96
gi|23380021|gb|AAM82920.1|
                              polymerase [Hepatitis B virus]
                                                                       351
                                                                             3e-96
gi 23379934 gb AAM82862.1
                              polymerase [Hepatitis B virus] >...
                                                                       350
                                                                             8e-96
gi|23380036|gb|AAM82930.1|
                              polymerase [Hepatitis B virus]
                                                                       349
                                                                             1e-95
gi 23380156 gb AAM83010.1
                              polymerase [Hepatitis B virus]
                                                                       349
                                                                             1e-95
gi 23379922 gb AAM82854.1
                              polymerase [Hepatitis B virus]
                                                                       349
                                                                             1e-95
gi 23379943 gb AAM82868.1
                              polymerase [Hepatitis B virus]
                                                                       349
                                                                             1e-95
gi 23379967 | gb | AAM82884.1 |
                              polymerase [Hepatitis B virus]
                                                                       349
                                                                             1e-95
gi 23379928 gb AAM82858.1
                              polymerase [Hepatitis B virus]
                                                                       349
gi | 23380057 | gb | AAM82944.1 |
                              polymerase [Hepatitis B virus]
                                                                       348
                                                                             2e-95
gi 23379925 gb AAM82856.1
                              polymerase [Hepatitis B virus] >...
                                                                       348
                                                                             Że-95
gi|23380141|gb|AAM83000.1|
                              polymerase [Hepatitis B virus]
                                                                       348
                                                                             2e-95
gi|23380165|gb|AAM83016.1|
                              polymerase [Hepatitis B virus]
                                                                       348
                                                                             2e-95
gi | 23379997 | gb | AAM82904.1 |
                              polymerase [Hepatitis B virus]
                                                                       348
                                                                             3e-95
gi | 23380147 | gb | AAM83004.1 |
                              polymerase [Hepatitis B virus] >...
                                                                       348
                                                                             3e-95
gi | 23379868 | gb | AAM82818.1 |
                              polymerase [Hepatitis B virus] >...
                                                                       348
                                                                             3e-95
gi 23379958 gb AAM82878.1
                              polymerase [Hepatitis B virus] >...
                                                                       348
                                                                             3e-95
gi 23379904 gb AAM82842.1
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             3e-95
gi 23379931 gb AAM82860.1
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             3e-95
gi|23380159|gb|AAM83012.1|
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             3e-95
gi | 23380144 | gb | AAM83002.1 |
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             3e-95
gi 23379892 gb AAM82834.1
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             4e-95
gi 23380000 gb AAM82906.1
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             4e-95
gi | 23380042 | gb | AAM82934.1 |
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             4e-95
gi|23380003|gb|AAM82908.1|
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             5e-95
gi|23379886|gb|AAM82830.1|
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             5e-95
gi | 23380009 | gb | AAM82912.1 |
                              polymerase [Hepatitis B virus] >...
                                                                       347
                                                                             6e-95
gi | 23380153 | gb | AAM83008.1 |
                              polymerase [Hepatitis B virus]
                                                                       347
                                                                             6e-95
gi|23379973|gb|AAM82888.1|
                              polymerase [Hepatitis B virus] >...
                                                                       347
                                                                             6e-95
gi 23380045 gb AAM82936.1
                              polymerase [Hepatitis B virus]
                                                                       346
                                                                             7e-95
gi|23379877|gb|AAM82824.1|
                              polymerase [Hepatitis B virus] >...
                                                                       346
                                                                             8e-95
gi | 23380138 | gb | AAM82998.1 |
                              polymerase [Hepatitis B virus]
                                                                       346
                                                                             9e-95
gi | 23379871 | gb | AAM82820.1 |
                              polymerase [Hepatitis B virus]
                                                                       346
                                                                             9e-95
gi | 23380162 | gb | AAM83014.1 |
                              polymerase [Hepatitis B virus]
                                                                       346
                                                                             9e-95
gi 23379946 | gb | AAM82870.1 |
                              polymerase [Hepatitis B virus] >...
                                                                       346
                                                                             9e-95
gi 23379895 gb AAM82836.1
                              polymerase [Hepatitis B virus]
                                                                       346
                                                                             1e-94
gi | 23379913 | gb | AAM82848.1 |
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                             le-94
gi | 23379916 | gb | AAM82850.1 |
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                             le-94
gi|23379991|gb|AAM82900.1|
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                             le-94
gi 23380012 | gb | AAM82914.1 |
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                             1e-94
gi | 23379889 | gb | AAM82832.1 |
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                            1e-94
gi|23379949|gb|AAM82872.1|
                              polymerase [Hepatitis B virus]
                                                                       345
                                                                            le-94
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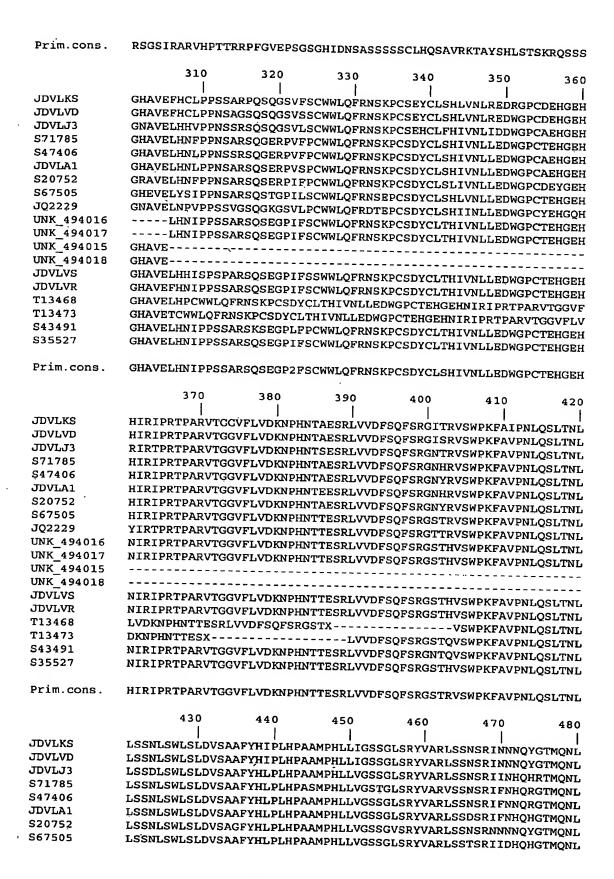
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gi | 23380039 | gb | AAM82932.1 |
                             polymerase [Hepatitis B virus]
                                                                      345
                                                                           1e-94
gi | 23379898 | gb | AAM82838.1 |
                             polymerase [Hepatitis B virus]
                                                                      345
                                                                           2e-94
gi|23379880|gb|AAM82826.1|
                             polymerase [Hepatitis B virus]
                                                                      345
                                                                           2e-94
gi | 23380033 | gb | AAM82928.1 |
                             polymerase [Hepatitis B virus]
                                                                      345
                                                                           2e-94
gi | 23379874 | gb | AAM82822.1 |
                             polymerase [Hepatitis B virus]
                                                                      344
                                                                           3e-94
gi 23379979 | gb | AAM82892.1 |
                             polymerase [Hepatitis B virus]
                                                                      344
                                                                           3e-94
gi|23380015|gb|AAM82916.1|
                             polymerase [Hepatitis B virus]
                                                                      344
                                                                           4e-94
gi | 23379937 | gb | AAM82864.1 |
                             polymerase [Hepatitis B virus]
                                                                      344
                                                                           4e-94
gi | 23379940 | gb | AAM82866.1 |
                             polymerase [Hepatitis B virus] >...
                                                                      343
gi 23380054 | gb | AAM82942.1 |
                             polymerase [Hepatitis B virus]
                                                                      343
gi 23379910 | gb | AAM82846.1 |
                             polymerase [Hepatitis B virus]
                                                                      343
                                                                           7e-94
gi 23379901 | gb | AAM82840.1 |
                             polymerase [Hepatitis B virus]
                                                                      343
                                                                           8e-94
gi | 23380018 | gb | AAM82918.1 |
                             polymerase [Hepatitis B virus]
                                                                      343
                                                                           9e-94
gi 23380027 | gb | AAM82924.1 |
                             polymerase [Hepatitis B virus]
                                                                      342
                                                                           1e-93
gi | 1914714 | emb | CAA66689.1 |
                             polymerase [Hepatitis B virus]
                                                                      342
                                                                           le-93
gi|23379982|gb|AAM82894.1| polymerase [Hepatitis B virus]
                                                                      342
                                                                           2e-93
gi|5019986|gb|AAD37962.1| P protein [Hepatitis B virus]
                                                                      341
                                                                           2e-93
gi|23380051|gb|AAM82940.1| polymerase [Hepatitis B virus]
                                                                      341
                                                                           2e-93
gi|27450186|gb|AA014550.1|AF460223_1 polymerase [Hepatitis ...
                                                                     341
                                                                           3e-93
gi|5019949|gb|AAD37932.1| P protein [Hepatitis B virus]
                                                                      341
                                                                           4e-93
gi|27450210|gb|AA014562.1|AF460235_1 polymerase [Hepatitis ...
                                                                      338
gi|27450206|gb|AA014560.1|AF460233_1 polymerase [Hepatitis ...
                                                                      337
                                                                           4e-92
gi|1107593|emb|CAA56885.1| polymerase [Hepatitis B virus]
                                                                      336
                                                                           7e-92
gi|27450208|gb|AA014561.1|AF460234_1 polymerase [Hepatitis ...
                                                                      336
                                                                           8e-92
gi|27450182|gb|AA014548.1|AF460221_1 polymerase [Hepatitis ...
                                                                      336
                                                                           8e-92
gi|27450184|gb|AA014549.1|AF460222_1 polymerase [Hepatitis ...
                                                                      335
                                                                           2e-91
gi 3820918 emb CAA08937.1 polymerase [Hepatitis B virus] >...
                                                                      332
                                                                           2e-90
gi|3820942|emb|CAA08951.1| polymerase [Hepatitis B virus]
                                                                      330
                                                                           5e-90
gi|3820933|emb|CAA08947.1| polymerase [Hepatitis B virus]
                                                                           8e-89
                                                                      326
gi 3820945 emb CAA08953.1 polymerase [Hepatitis B virus]
                                                                      326
                                                                           9e-89
gi 3820930 emb CAA08945.1 polymerase [Hepatitis B virus]
                                                                      325 3e-88
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BLASTP 2.2.5 (Nov-16-2002) (Altschul, S.F., et al., "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402 (1997)) against HBV subtype sequence S20757, cutoff = 3e-88 (to select human sequences).

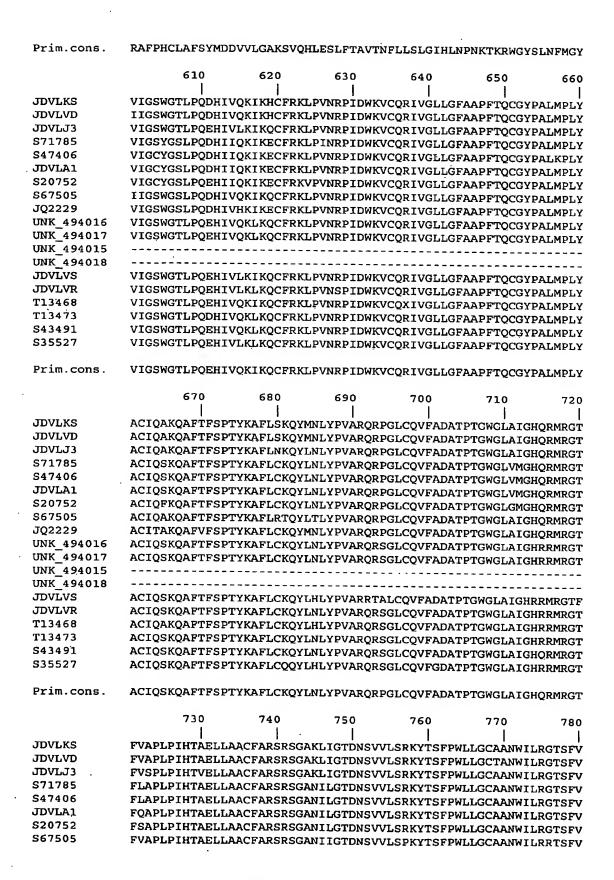
	bottom delignment of 15 mbv polymerase sequences
	10 20 30 40 50 60
JDVLKS	MPLSYQHFRKLLLLDDGTEAGPLEEELPRLADADLNRRVAEDLNLGNLNVSIPWTHKVGN
JDVLVD	MPLSYQHFRKLLLLDDGTEAGPLEEELPRLADADLHRRVAEDLNLGNLNVSIPWTHKVGN
JDVLJ3	MPLSYQHFRKLLLLDDEAGPLBEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
.·S71785	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEDLNRRVAEDLNLGNLNVSIPWTHKVGN
S47406	MPLSYQHFRRLLLLDDEAGPLEEELPRLADEDLNRRVAEDLNLGNLNVSIPWTHKVGN
JDVLA1 .	MPLSYQHFRRLLLLDDEAGPLEEELPRLADEGLNRHVAEELNLGNLNVSIPWTHKVGN
S20752	MPLSYQHFRRLLLLDDEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
S67505	MPLSCPHFRKLLLLDE EAGPLEEELPRLADEGLNRRVAEDLNLQLPNVSIPWTHKVGN
J02229	MPLSYPHFRKLLLLDDEAGPLEEELPRLADEDLNRRVAADLNLQLPNVSIPWTHKVGN
UNK 494016	TO THE TOTAL WAS A TOTAL OF THE
UNK 494017	
UNK 494015	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
UNK 494018	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
JDVLVS	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEDLNRRVAEDLNLGNLNVSIPWTHKVGN
JDVLVR	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
T13468	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
T13473	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEDLNRRVAEDLNLGNLNVNIPWTHKVGN
, \$43491	MPLSYQHFRKLLLLDNEAGPLEEELPRLADEDLNRRVAEDLNLGNLNVSIPWTHKVGN
\$35527	MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRVAEDLNLGNLNVSIPWTHKVGN
	THE PERSON OF TH
Prim.cons.	MPLSYQHFRKLLLLDDGTEAGPLEEELPRLADEGLNRRVAEDLNLGNLNVSIPWTHKVGN
	DESCRIPTION OF THE PROPERTY OF
	70 80 90 100 110 120
JDVLKS	FTGLYSSTAPIFNPEWQTPSFPKIHLQEDIINRCQQFVGPLTVNEKRRLKLIMPARFYPT
JDVLVD .	FTGLYSSTVPIFNPEWQTPSFPKIHLQEDIINRCQQFVGPLTVNEKRRLKLIMPARFYPT
JDVLJ3	FTGLYSSTVPSFNPQWQTPSFPDIHLQEDIINKCKQFVGPLTVNEKRRLKLIMPARFYPN
S71785	FTGLYSSTVPVFNPHWKTPSFPNIHLHQDIIKKCEQFVGPLTVNEKRRLQLIMPARFYPN
S47406	FTGLYSSTVPVFNPHWKTPSFPNIHLRQDIIKKCEQFVGPLTVNEKRRLQLIMPARFYPK
JDVLA1	FTGLYSSTVPVFNPHWKTPSFPNIHLHQDIIKKCEQFVGPLTVNEKRRLQLIMPARFYPK
S20752	FTGFYSSTVPVFNPHWETPSFPNIHLHQDIIKKCEQFVGPLTVNEKRRLQLIMPARFYPK
S67505	FTGLYSSTVPVFNPKWQTPSFPDIHLHQDIINKCEQFVGPLTVNEKRRLKLIIAARFYPN
JQ2229	FTGLYSSTVPAFNPNWSTPSFPDIHLHQDLISKCEQFVGPLTKNELRRLKLVMPARFYPK
UNK 494016	
UNK 494017	
UNK 494015	FTGLYSSTVPVFNPDWKTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
UNK 494018	FTGLYSSTVPVFNPDWKTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
JDVLVS	FTGLYSSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPK
JDVLVR	FTGLYSSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
T13468	FTGLYSSTVPVFNPEWQTPSFPNIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
T13473	FTGLYSSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
S43491	FTGLYSSTVPVFNPEWKTPSFPNIHLQEDIIDRCQQYVGPLTVNEKRRLKLIMPARFYPN
S35527	FTGLYSSTVPVFNPECQTPSFPNIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPN
L	The state of the s
Prim.cons.	PTGLYSSTVPVFNPEWQTPSFPNIHLQEDIINRCQQFVGPLTVNEKRRLKLIMPARFYPN
	130 140 150 160 170 180
JDVLKS	HTKYLPLDKGIKPYYPDQVVNHYFQTRHYLHTLWKAGILYKRETTRSASFCGSPYSWEQE
JDALAD	HTKYLPLDKGIKPYYPDQVVNHYFQTRHYLHTLWKAGILYKRETTRSASFCGSPYSWEOE
JDVLJ3	VTKYLPLDKGIKPYYPEHVVNHYFQTRHYLHTLWKAGILYKRETTRSASFCGSPYSWEOE
S71785	VTKYLPLDKGIKPYYPEHLVNHYFQTRHYLHTLWKAGILYKRETTRSASFCGSPYSWEOE
S47406	VTKYLPLDKGIKPYYPEHLVNHYFQTRHYLHTLWKAGILYKRETTHSASFCGSPYSWEGE
JDVLA1	VTKYLPLDKGIKPYYPEHLVNHYFQTRHYLHTLWKAGVLYKRETTHSASFCGSPYSWEOE
S20752	VTKYLPLDKGIKPYYPEHLVNHYFQTRHYLHTLWKAGILYKRETTHSASFCGSPYSWEOD
S67505	APKYLPLDKGIKPYYPEHVVNHYFQTRHYLHILWKAGILYKRETTRSASFCGSPYSWEQE

Table 21: CLUSTALW alignment of 19 HBV polymerase sequences

JQ2229	VTKYFPMDKGIKP	YYPBHAVNHYR	KTRHYLHTI.	WKAGTI.VVDEC	TREACTION	D1/4/170-
UNK_494016					TRSASFCGS	PISWEQE
UNK_494017						
UNK_494015	LTKYLPLDKGIKP	YYPBYAVNHYF	KTRHYLHTL	WKAGILYKRET	TRSASECGS	DVGMEOR
UNK_494018	PIKATAPPDKGIKA	A A B B A W A M H A E	KTRHYLHTLI	WKAGILYKRET	TRSASFCGS	DVCMEOR
JDVLVS	PIKIPPPDKGIKE	YYPEHAVNHYF	KTRHYLHTL	WKAGILYKRET	TRSASECGS	DVCWEOR
JDVLVR	PLKATATORGIKA	YYPEHAVNHYF	KTRHYLHTL	WKAGILYKRET	TRSASECGS	DVCWEAR
T13468	PIKAPPDKGIKD	YYPEHAVNHYF	KTRHYLHTLI	WKAGILYKRET	TRSASFCCS	DVCWEOR
T13473	PIKAPPPDKGIKD	YYPEHAVNHYF	KTRHYLHTL	WKAGILYKRET	TRSASECCS	DVCMEOR
S43491	PIKAPPDKG1 Kb	YYPEHAVNHYF	'QTRHYLHTLI	WKAGILYKRET	TRSASECES	DVCWEOR
\$35527	LTKYLPLDKGIKP	YYPEHAVNHYF	KTRHYLHTL	WKAGILYKRET	TRSASFCGS	PYSWEQE
Prim.cóns.	LTKYLPLDKGIKP	YYPBHAVNHYF	'QTRHYLHTL	∜KAGIĻYKRET	TRSASFCGS	PYSWEQE
	190	200	210	220	230	240
JDVLKS	I OHGDI VI KTGODI	ICDECEGGODO				
JDVLVD	LOHGRLVIKTSORI	ICDESFUSQPS	GILSRSSVGI	PCIRSQLKQSR	LGLQPHQGP:	LASSQPG
JDVLJ3	LOHGRIVIATSORI	ICDVCEDDOGG	GILSRSSVG	PCIRSQLKQSR	LGLQPRQGR:	LASSQPS
`S71785	LOHG	APCPUOOCC	GILSKSPVG	CIQSQLRQSR	LGPQPTQGQ:	LAGLQQG
S47406	LOHG	- AESFHQQSS	GILSRPPVGS	SSLQSKHRKSR	LGLQSQQGH	LARRQQG
JDVLA1	LOHG	- YESEROOCC	GILSRPPVGS	SLOSKHSKSR	LGLQSQQGH1	LARRQQG
S20752	LOHG	-MESTHOOSS	GILSRPPVGS	SSLQSKHCKSR	LGLQSQQGL1	LARRQQG
S67505	LOHG	- VEDACOUCT	GILSKPPVGS	SSLQSKHRKSR	LGLQSQQGH)	LARRQQG
JQ2229	LOHG	CTEST CAOSE	GILPRASVGS	SPVQSQLKQSR	LGLQSQQRQ	LARSHQG
UNK 494016	LQHGSTSLNDTKR	CCONDUCACOS	GILSKPSAGS	SATOSKFOOSR	LGLQHKQGQ1	LANGKQG
UNK 494017						
UNK 494015	LOHGRIVFOTSTRE		CTI CDCDVQT	OTT COL VOCA		
UNK 494018	LOHGRLVFOTSTRE	IGDESECEVEE	GITOKOLAGE	CAKSOTKOSK	rerőbőőesi	LARGKSG
JDVLVS	LQHGRLVFQTSTRE	IGDESECSOSS IGDESECSOSS	GILSKSPVGF	CARSOTKOSK	LGLQPQQGS]	ARGKSG
JDVLVR	LOUGHLUFOTOTH	IGDESFCSQSS IGDESFCSQSS	GILSKSPVGF	CARSOTKOSK CARSOTKOSK	LGLQPQQGS1	ARGKSG
T13468	LOHGRLVFOTSTRH	IGDESECSOSS	GILSKSPVGP GILSKSPVGP	CARSOTKOSE.	LGLQPQQGSI	MARGKSG
T13473	LOHGRLVFQTSTRH	IGDKSFCS0SS	GTLSRSPVGF GTLSpepver	GAKZÕTKÕZK GAKZÕTKÕZK	LGLQPQQGSI	LARGKSG
S43491	LOHGRLVFQTSTRH	GDESECSOSS	GTI.SPSDVGT	CARSOT KOCK	rerobódesi	ARGQSG
\$35527	LQHGRLVFQTSTRH	GDESFCSQSS	GILSRSPVGP	CVRSQLKQSR CVRSQLKQSR	rgrð þóðgsi rgrð þóðgsi	LARRINGG
Prim.cons.	LQHGRLVFQTSTRH	GDESFCSQSS	GILSRSPVGP	CVRSQLKQSR	LGLQPQQGS1	ARGQQG
	250	260	270	280	290	300
TD:17 ***				1	1	1
JDVLKS	RSGSIRARVHPSTR	RCFGVEPSGS	GHVDPSVNNS	SSCLRQSAVRI	KAAYSHLSTS	KROSSS
JDVLVD	KOGOTKAKAHPOTK	RYFGVEPSGS	GHIDHSVNNS	SSCLHOSAVRI	YAAVSHT.STC	KDOCCC
JDVLJ3	GSGSTRAGIHSTPW	GIAGARBSSS	GHTHNCANSS	SSCLHOSAVRI	YE'A VEDWeme	VDUCCC
S71785	RSWSIRAGIHPTAR	RPFGVEPSGS	GHNTNLASKS	ASCIYOSPVRI	ΚΑΑΥΡΑΝΙΟΨΕ	PVUCCC
S47406	KOMOTKAGIHLIAK	RPFGVEPSGS	GHNTNLASKS	ASCLYOSPVRI	CAAVDAVCTE	EVUCCC
JDVLA1	KOWSTRAGIHPTAR	RPFGVEPSGS	GHTTNLASKS	ASCLHOSPVR	<i>(1) TYDSWETE</i>	PYUCCC
S20752	WSWSIRAGTHPTAR	RPFGVEPSGS	GHTTHRASKS	ASCLYOSPDRE	CATVPGVCTE	PDUCCO
\$67505 JQ2229	REGSTRARVHSTTR	RSFRVELSGS	GSNHNIASTS	SSCRHOSAVRI	TAVSHI, STO	PDUCCC
-	KPCKTKPKAHLLALK	WPAGVEPSST	RCVNNLASRS	ASCEHOSAVRI	EKANDST.CTC	VDUTCT
UNK_494016			- 			
UNK_494017	2000					
UNK_494015	RSGSIWSRVHPTTR	RPFGVBPSGS	GHIDNTASST	SSCLHQSAVRI	CTAYSHLSTS	KRQSSS
UNK_494018	REGETWERVHPTTR	RPFGVEPSGS(GHIDNTASST	SSCLHOSAVRE	TAVCHI.CTC	KBOCCC
JDVLVS	KOGOTKAKABALIK	RSFGVEPSGS(3HIDNRASST	SSCLHOSAVRI	(ΤΔΥΟΝΤ.ΟΤΟ	KDOGGG
JDVLVR	KSGSIKAKVHPTIK	RSFGVBPSGS(GHIDNSASST	SSCLHOSAVRI	(ΤΔΥΩΗΙ.ΩΤΩ	KDOCCC
T13468	KSGSTKAKVHPTTK	RSFGVBPSGS(GHIDNSARSA	SSCLHOSAVRE	TAVSHI,STS	KDOCCC
T13473	KIGŚIKAKAHPIIK	RSFGVBPSGS(GHIDNSASSP	SSCLHOSAVRE	TAYCHI.STT	KDOCCC
S43491 S35527	ROGSTRARVHPTTR	RPFGVBPSGS(3HIDNSASSA	SSCFHOSAVRE	CTAYSHLSTS	KROCCC
533321	RSGRLRARVHPTTR	KSFGVEPSGS(SHLDNSASSS	SSCLHQSAVR	CTAYSHLSTS	KRQSSS



JQ2229	LSSNLSWLSLDVSA	AFYHLPLHPA	AMPHLLVGSSC	LSRYVARLS	STSRIHDHO	HGTLONI.
UNK_494016	PS2NP2MP2PDA2	ЧЕЛНТЫТНЬ Ў	AMPHLLVGSSC	I.PRYVAPI.C	STSDNITHY	COTHONIT.
UNK_494017	LSSNLSWLSLDVSA	AFYHIPLHPA	AMPHLLVGSSG	LPRYVARLS	STSRNINYQ	HGTMQNL
UNK_494015 UNK_494018						
JDVLVS	LCCNI CWI CI DUCA	ADMITOLISM				
JDVLVR	LSSNLSWLSLDVSA	YEANT DI 11DY YE IHT PPH PV	AMPHLLVGSSG	LPRYVARLS	STSRNINHQ	HGTMQDL
T13468	LSSNLSWLSLDVSA	VEANT DITALEM VETUT STUDY	AMPHLLVGSSG	LPRYVARLS	STSRNINHQ	HGAMQDL
T13473	LSSNLSWLSLDVSA LSSNLSWLSLDVSA	AFYHTDI.UDA	MUNITARIA MUNITARIA	LPRYVARLS	STSRNXNYQ	HGTMQDL
S43491	LSSNLSWLSLDVSA	AFYHTPI.HPA	MDHT.T.VCCCC	PERMINANTO	STSRNINXQ	HGTMQDL
S35527	LSSNLSWLSLDVSA	AFYHIPLHPA	AMPHLLVGSSG	LPRYVARLS	STSRNINYQI STSRNINYQI	HGTMQDL HGTMQDL
Prim.cons.	LSSNLSWLSLDVSA	AFYHIPLHPA	AMPHLLVGSSG	LSRYVARLS	STSRNINHQI	HGTMQNL
	490 1	500	510	520	530	540
JDVLKS	HDSCSROLVVSLML	LVKTVCMPI III	VCUDIU CDD		·	- 1
JDVLVD	HDSCSRQLYVSLML	I.VKTVGWKLH	PISHPINICES	KIPMGVGLS	PFLLAQFTS	AICSVVR
JDVLJ3	HDSCSRNLYVSLML	LYKTYGRKI.HI	ULSULTIONS.	KIDMCACTC	PFLLAQFTS	AICSVVR
`\$71785	HDYCSRNLYVSLLL	LYOTFGRKLH	LYSHPITLGFR	KIPMGVGLS	PELLACETS	AICSVVR
S47406	HDYCSRNLYVSLLL	LYOTFGRKLH	LYSHPITLGFR	KIPMGVGLS	PFLLAQFTS/	AICSVVR
JDVLA1	HDSCSKNPA ASPPP	LYQTFGRKLHI	LYSHPIILGFR	KIPMGVGLS	PFI.I.AOPTC7	TOCKED
S20752	UDSC2KOPA A2PWP	LYQNFGWKLHI	JYSHPIVLGFR	KIPMGVGT.S	DELLACETCE	TCCIG
S67505	UNICSKNIE VSTWP	LYKTFGRKLHI	LYSHPIVLGFR	KTPMGVGT.S:	PRIJ.AOPTCC	TOOLD
JQ2229	HNSCIRNLYVSLLL	LFQTLGRKLHI	LYSHPIILGFR	KIPMGVGLS	PFI.I.AOFTC2	TCCIAD
UNK_494016	UDSCSKNTA ARPTE	LYKTFGRKLHI	LYSHPIILGFR	KIPMGVGLS	PFI.I.AOPTG7	TCCIAD
UNK_494017	HDSCSRNLYVSLLL	LYKTFGRKLHI	LYSHPIILGFR	KIPMGVGLS	PFLLAQFTSA	ICSVVR
UNK_494015 UNK 494018						
JDVLVS	UDCCCDNI VIOLET					
JDVLVR	HDSCSRNLYVSLLL	PAKILLGKKTHI	YSHPIILGFR	KIPMGGGLS	PFLLAQFTS	ICSVVR
T13468	HDSCSRNLYVSLLL	LYVTECTVIII	YSHPIILGFR	KIPMGVGLS	PFLLAQFTS <i>F</i>	ICSVVR
T13473	HESCSRNLYVSLLLI HDSCSKHLYVSLLLI	VKTEGRKLHI	YEDITTIGER.	KIPMGVGLS	PFLLAQFTSA	ICSVVR
S43491	HDSCSKHLYVSLLLI	LYKTEGRKLHI	VSUDITIOUSY.	KIPMGVGLSI	PFLLAQFTSA	ICSVVR
S35527	HDSCSRNLYVSLLL	/YKTFGRKLHI	YSHPIILGFR	KIPMGVGLSI	PFLLAQFTSA PFLLAQFTSA	ICSVVC
Prim.cons.	HDSCSRNLYVSLLLI	LYKŢFGRKLHI	YSHPIILGFR	KIPMGVGLSI	PFLLAQFTSA	ICSVVR
	550	560	550			
	1	360	570 I	580	590	600
JDVLKS	RAFPHCLAFSYMDD	VI GAKSVOHE	 PPI.VTAVTNE	 		
JDVLVD	RAFPHCLAFSYMDD	/VLGAKSVOHR	ESLYTAUTNE	CT STGININI	PNKTKRWGYS	LNFMGY
JDVLJ3	RAPPHCLAPS YMDD\	/VLGAKSVOHT	EST.VAAVTME:	LI.CI CTUTAII	A ramian range	T
S71785	RAFPHCLAFSYMDD	/VLGAKSVQHL	ESLFTAVTNF	LLSLGTHLNI	NKTKDWCVC	LUEMOV
S47406	MAT FITCHAT STRIDU	ATRICATOR AND A MANAGEMENT	ESLFTAVTNF	LLSLGTHINI	NKTKDWCVC	LMDMOV
JDVLA1	KAFPHCLAFSYMDD(/VLGAKTVHHI	ESLFTAVTNF	LLSLGTHLNI	NKTKDWCVC	LUDMOV
S20752	RAFPHCLAFSYMDD(/VLGAKSVQHI	ESLFTAVTNFI	LLSLGTHING	ΝΚΤΚΌΜΩνο	LUDMOV
S67505	RAP PHCLAPS IMDUL	JVLGAKSVQHI	ESIYTAVTNFI	LLSLGTHLNE	NKTKDWGVC	LMEMOV
JQ2229	KAPPHCLAFSYMDDI	JVLGAKSVQHL	ESLYTAVTNFI	LSVGTHINT	CKTKPWCVC	LUEMOV
UNK_494016	RAP PHCLAF 5 YMDDV	/VLGAKSVOHL	ESLFTSITNFI	J.SLGTHI.NI	MKTKDWCVC	I MEMORY
UNK_494017 UNK 494015	KAI PHCLAI SYMDDV	/VLGAKSVQHL	ESLFTSITNFI	LLSLGIHLNI	NKTKRWGYS	LNFMGY
UNK 494018		·			. 	
JDVLVS	PARDUCI ARCUMDO					
JDVLVR	RAFPHCLAFSYMDDY	VIIGAKSVQHL	ESLFTSITNFI	LSLGIHLNE	NKTKRWGYS	LNFMGY
T13468	RAFPHCLAFSYMDDY	VII'CD KENUM APPRINZAČITI	ESLETSITNFI	LSLGIHLNE	NKTKRWGYS	LNFMGY
T13473	RAFPHCLAFSYMDDV RAFPHCLAFSYMDDV	A DOWYS A ÓUT	EDI.VTOTTNEI	JUSTGIHTNE	HKTKRWGYS	LNFMGY
S43491	RAFPHCLAFSYMDDV	VLGAKSVONI	ESI ETCITNEI	JUSUGIHLNE	NKTKRWGYS	LNFMGY
S35527	RAFPHCLAFSYMDDV	VLGAKSVOHL	ESLFTSTTNE	TSLCIAININE	MKAKBMGAS	PNEWGY
			· · · · · · · · · · · · · · · · · · ·	Gramb	MALARWOIS	THEMGY



JQ2229	FVAPLPIHTAELLA	ACFARSRSGA	TLIGTONSV	/T.SRKYTSFDW	T.T.CCA A MUST	DOTODU
UNK_494016	FVAPLPIHTAELLAACFARSRSGATLIGTDNSVVLSRKYTSFPWLLGCAANWILRGTSFV FVAPLPIHTAELLAACFARSRSGAKLIGTDNSVVLSRKYTSFPWLLGCAANWILRGTSFV					
UNK_494017	FVAPLPIHTAELLAACFARSRSGAKLIGTDNSVVLSRKYTSFPWLLGCAANWILRGTSFV					
UNK_494015						
UNK_494018		-				
JDVLV\$	VAPLPIHTAELLAA	CFARSRSGAK	LIGTDNSVVI	SRKYTSFPWI	I.GCAANWTI.E	CTVEVV
JDVLVR	LANDLINTATELLY	ACFARSRSGA	KLIGTDNSVV	LSRKYTSFPW	LLGCAANWTI	DOTO EV
T13468	L AND DITH LARD LA	ACFARSRSGA	$\mathtt{KLIGTDNSVV}$	/LSRKYTSFPW	LLGCAANWTI	DOTODU
T13473	F.ANDLDIHLWETTY	ACFARSRSGA	KLIGTDNSVV	LSRKYTSFPW	LLGCA A MUTT	ретери
S43491	FVAPLPIHTAELLAACFARSRSGATLIGTDNSVVLSRKYTSFPWLLGCAANWILPGTSFV					
S35527	FVAPLPIHTAELLA	ACFARSRSGA	KLIGTDNSVV	LSRKYTSFPW	LLGCAANWTT	RGTSEV
Prim.cons.						
PIIM.CONS.	FVAPLPIHTAELLAACFARSRSGAKLIGTDNSVVLSRKYTSFPWLLGCAANWILRGTSFV					
	790	800	810	820	830	840
JDVLKS	VIIDENI NIDADDDOOD	anz az anna -		l	ļ	1
JDVLVD	YVPSALNPADDPSR	GRUGUSRPLU	RLPFQPTTGR	TSLYAVSPSV	PSHLPVRVHF	TASPLHV
JDVLJ3	YVPSALNPADDPSR	GRLGLSRPLL.	RLPFQPTTGR	TSLYAVSPSV	PSHLPVRVHF	'ASPLHV
S71785	YVPSALNPADDPSR	GRLGLYRPLL	RLPYRPTTGR	TSLYADSPSV	PSHLPDRVHF	'ASPLHV
S47406	YVPSALNPADDPSRO	SRLGIFRPLL.	RLPFRPTTGR	TSLYADSPSVI	PSHLPVRVHE	'ASPLHV
JDVLA1	YVPSALNPADDPSRO	SKIGLSKPLL:	RLPFRPTTGR	TSLYADSPSVI	PSHLPDRVHF	'ASPLHV
S20752	YVPSALNPADDPSRO	SKLGLSKPLLI	RLPFRPTTGR	TSLYADSPSVI	PSHLPDRVHF	'ASPLHV
S67505	YVPSALNPADDPSRO	SKEGESKPEE	CLPFRPTTGR	TSLYADSPSVI	PSHLPDRVHF	'ASPLHV
JQ2229	YVPSALNPADDPSRO	SPIGLINDITI	RPWFRPTTGR	TSLYAVSPSVI	PSHLPVRVHF	ASPLHV
UNK 494016	YVPSALNPADDPSRO	TOI CI VODI TI	KT DED DEED SE	TSLYADSPSVI	PSHLPDRVHF	'ASPLHV
UNK 494017	YVPSALNPADDPSRO YVPSALNPADDPSRO	SDICIVEDITE	HLPFRPTTGR	TSLYAVSPSVI	PSHLPDRVHF	'ASPLHV
UNK 494015	\		HLPFRPTTGR	TSLYAVSPSVI	PSHLPDRVHF	ASPLHV
UNK 494018						
JDVLVS	VPSALNPADDPSRGF	מו.מו.דססו ד עו		CI Vavonovino		
JDVLVR	YVPSALNPADDPSRO	PI.CI.VPDI.T.I	L.DEDDTTON	SLIAVSPSVPS	SHLPDRVHFA	SPLHVA
T13468	YVPSALNPADDPSRO	DI.CI.VDDI.I	JUPERPITCH JI.DEDDTTCD	TSLYAVSPSVE	SHLPDRVHF	ASPLHV
T13473	YVPSALNPADDPSRO	RIGI.VPDI.I.	11.DFFRF11GR	TSLIAVSPSVE	SHLPDRVHF	ASPLHV
S43491	YVPSALNPADDPSRO	RIGI.VPDI.T.	TOPPRETIGE	TOLVAVSPSVE	SHLPDRVHF	ASPLHV
S35527	YVPSALNPADDPSRO	RIGI.VPDI.I.	II.DEODTTCD:	TSLYAVSPSVE	SHLPDRVHF	ASPLHV
			IDETQETIGR	TODIAVSPSVE	SHLPVRVHF	ASPLHV
Prim.cons.	YVPSALNPADDPSRG	RLGLYRPLLF	RLPFRPTTGR:	TSLYAVSPSV F	SHLPDRVHF	ASPLHV
JDVLKS	Aumpo					
JDVLVD	AWRPP					
JDVLJ3	AWRPP					
S71785	AWRPP					
S47406	AWRPP					
JDVLA1	AWRPP					
S20752	AWRPP					*
S67505	AWRPP					
JQ2229	AWRPP AWRPP	>				
UNK 494016	AWRPP	•				
UNK_494017	AWRPP					
UNK_494015	AWKPP			•		
UNK 494018						
JDVLVS	WRPP-					
JDVLVR	AWRPP					
T13468	AWRPP					
T13473	AWRPP					
S43491	AWRPP					
\$35527	AWRPP					
Prim.cons.	AWRPP		•		•	

CLUSTALW alignment of 19 HBV polymerare sequences representing the sybtypes adw (4), ayw (5), ayr (4) and adr (6) (NPS@: Network Protein Sequence Analysis, TIBS Vol. 25, No 3 (291):147-150, Combet C., Blanchet C., Geourjon C. and Deléage G. (March 2000))

CLUSTALW options used :
endgaps=1
gapdist=8
gapext=0.2
gapopen=10.0
hgapresidues=GPSNDQERK
ktuple=1
matrix=gonnet
maxdiv=30
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score=percent
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Table 22. HCV Multiple Sequence Alignment GCG Multiple Sequence File. Written by Omiga 1.1

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Name: HCV K1 R3
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HC_C2 MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR

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  HCV_J483 MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
    HCV_J8 MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
   HCV_JK1 MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
    HCV_JS MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
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 HCV_K1_R3 MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
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 HCV_K1_S3 MSTNPKPQRQ TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
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    HPCJCG MSTNPKPQRK TKRNTNRRPQ DVKFPGGGQI VGGVYLLPRR GPRLGVRATR
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  HPCJK049 MSTLPKPQRI TKRNINRRPQ DVKFPGGGQI VGGVYVLPRR GPKLGVRAVR
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 HCV_J483 KTSERSQPRG WRQPIPKARR PEGRAWAQPG YPWPLYGNEG LGWAGWLLSP
   HCV_J8 KTSERSQPRG RRQPIPKDRR STGKSWGKPG YPWPLYGNEG CGWAGWLLSP
   HCV_JK1
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 HCV_K1_R3 KTSERSQPRG RRQPIPKVRR SEGRTWAQPG YPWPLYGNEG LGWAGWLLSP
 HCV K1 S1 KTSERSQPRG RRQPIPKARR PEGRAWAOPG YPWPLYGNEG LGWAGWLLSP
 HCV_K1_S2 KTSERSQPRG RRQPIPKARQ PEGRAWAQPG YPWPLYGNEG MGWAGWLLSP
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           KTSERSQPRG RRQPIPKARP SQGRTWGQPG YPWPLYGNEG CCWAGWLMSP
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 HCV K1 R2
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1101

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     HCV_J8 IFCHSKKKCD ELAAALRGMG VNAVAYYRGL DVSVIPTQGD VVVVATDALM
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   TypeV D IPCHSKKKCD EIASKLRGMG LNAVAYYRGL DVSVIPTTGD VVVCATDALM
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   HPCJCG GSMRIVGPKT CSNTWHGTFP INAYTTGPCT PSPAPNYSRA LWRVAAEEYV
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     Th580 GSMKITGPRM CSNTWHGTFP INATTTSPSV PVPAPNYKRA LWRVSAEEYV
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   TypeV_D GSMRLAGPRT CANMWYGTFP INEYTTGPST PCPSPNYTRA LWRVAANSYV
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     HC G9 EVRRLGDFHY ITGVTTDKIK CPCQVPSPEF FTEVDGVRLH RYAPPCKPLL
  HCU16326 EVTRVGDFHY VTGMTTDNVK CPCQVPAPEF FTEVDGVRLH RYAPACRPLL
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      Th580 EVERHGDRHY VVGVTADGLK CPCQVPGPEF FTEVDGVRIH RYAPPCKPLL
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    TypeV_D EVRRVGDFHY ITGATEDELK CPCQVPAABF FTEVDGVRLH RYAPPCKPLL
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   HCV JK1
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    D89815 GGNITRVESE NKIVILDSFE PLRABE.DER EVSAAAEILR KTR.KFPAAM
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  HCU16326 GGNITRVESE NKVVILDSFD PLRAED.DEG BISVPAEILR KSR.KFPPAL
 HCV_H_CMR GGNITRVESE NKVVILDSFD PLVAEE.DER EVSVPAEILR KSR.RFARAL
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           GGNITRVESE NKVVILDSFE PLHAEG.DER EISVAAEILR KSR.KFPSAL
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    HCV J8
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    HCV_JS GGNITRVESE NKVVILDSFD PLHAEE.DER EVSVAAEILR KSR.KFPPAL
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           GGNITRVESE NKVVILDSFE PIRAEE.DER EVSVPAEILR RSR.KFPAAM
      HPCJ
    HPCJCG GGNITRVESE NKVVILDSFD PIRAVE.DER EISVPAEILR KPR.KFPPAL
  HPCJK046 GGNITRVESE NKIVILDSFE PLKAEF.DDR EISVAAECHR PPRFKYPPAL
  HPCJK049 GSNITRVESE SKVVILDSFE PLRACD.DED ELSVAAECFK KPP.KYPPAL
   HPCJTA GGNITRVESE NKVVILDSFD PLRABE.DER EVSVAAEILR KSK.KFPPAL
    HPCJTB GGNITRVESE NKVVILDSFD PLRABE.DER EVSVAAEILR KSK.KFPPAL
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   HPCPOLP GGDVTRIESE SKVVVLDSLD PMVEER.SDL EPSIPSEYML PKK.RFPPAL
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           RKLGVPPLRA WRHRAWSVRA RLLARGGKAA ICGKYLFNWA VRTKLKLTPI
   HPCCGAA
           RKLGIPPLRA WRHRARAVRA KLIAQGGKAR ICGLYLFNWA VRTKTKLTPL
     HPCFG
           RKLGVPPLRA WRHRARSVRA KLLSQGGRAA TCGRYLFNWA VKTKLKLTPI
HPCGENANTI
           RKLGVPPLRV WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VKTKLKLTPI
  HPCGENOM
   HPCHUMR RKLGVPPLRV WRHRARSVRA RLLSQGGRAA TCGKYLFNWA VKTKLKLTPI
      HPCJ RKLGVPPLRV WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VRTKLKLTPI
    HPCJCG RKLGVPPLRV WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VKTKLKLTPI
  HPCJK046 RKLGAPPLRA WRHRARAVRA KLIAQGGKAA ICGMYLFNWA VKTKLKLTPL
  HPCJK049 RKLGIPPLRA WRHRARAVRA KLISQGGKAK ICGLYLFNWA VRTKAKLTPL
    HPCJTA RKLGVPPLRV WRHRARSVRA RLLSQGGRAA TCGKYLFNWA VRTKLKLTPI
           RKLGVPPLRV WRHRARSVRA RLLSQGGRAA TCGKYLFNWA VRTKLKLTPI
    HPCJTB
           RKLGCPPLRA WRHRARAVRA KLIAQGGRAK ICGLYLFNWA VRTKTKLTPL
    HPCK3A
 HPCPLYPRE
           RKLGVPPLRA WRHRARSVRA RLLARGGRAA ICGKYLFNWA VRTKLKLTPI
           RKLGAPPLRA WKSRARAVRA SLISRGGRAA VCGRYLFNWA VKTKLKLTPL
   HPCPOLP
           RKLGVPPLRV WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VKTKLKLTPI
     HPCPP
  HPCUNKCD RKLGVPPLRA WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VRTKLKLTPI
    MKC1A RKLGVPPLRV WRHRARSVRA KLLSQGGRAA TCGKYLFNWA VKTKLKLTPI
    NDM59 RKLGAPPLRA WKSRARAVRA SLISRGGRAA ICGRYLFNWA VKTKLKLTPL
     NZLI RKLGCPPLRA WRHRARAVRA KLIAQGGKAK ICGLYLFNWA VRTKTNLTPL
     SA13 RKLGVPPLRA WRHRARAVRA KLIAQGGKAA ICGIYLFNWA VKTKRKLTPL
    Th580
           RKLGAPPLRA WRHRARAVRA KLIAQGGKAA ICGKYLFNWA VKTKLKLTPL
           RKLGCPPLRA WRHRARAGRA KLIAQGGKAK ICGLYLFNWA VRTKTKLTPL
Type 3a CB
           RKLGCPPLRA WRHRARAVRA KLIAQGGKAK ICGLYLFNWA VRTKTNLTPL
   TypeV D
           RKLGAPPLRA WRHRARAVRA KLIAQGGKAA VCGKYLFNWA IKTKLRLTPL
     VN004
           RKLGAPPLRA WRHRARAVRA KLIAQGGKHA ICGKYLFNWA VRTKLKLTPL
    VN235
    VN405 RKLGAPPLRA WRHRARAVRA KLIAQGGGAA ICGKYLFNWA VKTKLKLTPI
          PAARLLDLSS WFTVSAGGGD IYHSVSRARP RLLLLGLLLL CVGVGIFLLP
    BEBE1
   D89815
           PEASQLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
ED43type_4
           PAAAKLDLSG WFTVGAGGGD IYHSMSHARP RYLLLCLLIL TVGVGIFLLP
```

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PAASRLDLSG WFVAGYGGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
     HC C2
            PSASQLDLSN WFTGGYSGGD IYHSVSHVRP RWFFWCLLLL SVGVGIYLLP
     HC G9
            PAASRLDLSG WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
  HCU16326
 HCV_H_CMR AAAGRLDLSG WFTAGYSGGD IYHSVSHARP RWFWFCLLLL AAGVGIYLLP
           AAAGRLDLSG WFTAGYSGGD IYHSVSHARP RWFWFCLLLL AAGVGIYLLP
    HCV J1
           PAASQLDLSG WFVAGYSGGD IYHSLSRARP RWFLLCLLLL SVGVGIYLLP
  HCV J483
           PEASRLDLSG WFTVGAGGGD IYHSVSHARP RLLLLCLLLL SVGVGIFLLP
    HCV J8
            PAASQLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
   HCV JK1
            PAASRLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
    HCV JS
 HCV K1 R1
            PAASQLDLSN WFVAGYSGGD VYHSLSRARP RWFMLCLLLL SVGVGIYLLP
            PAASQLDLSG WFVAGYSGGD IYHSVSRARP RWFMWCLLLL SVGVGIYLLP
 HCV K1 R2
 HCV K1 R3
            PAASQLDLSS WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVCVGIYLLP
            PAASQLDLSN WFVAGYSGGD VYHSLSRARP RWFMLCLLLL SVGVGIYLLP
 HCV_K1_S1
            PAASQLDLSG WFVAGYSGGD IYHSVSRARP RWFMWCLLLL SVGVGIYLLP
 HCV K1 S2
            PAASQLDLSS WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
 HCV K1 S3
            PAASRLDLSS WFVAGYSGGD IYHSVSHARP RWFMLCLLLL SVGVGIYLLP
    HCV_L2
           PAASQLDLSG WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
     HCV_N
            VSASKLDLSG WFVAGYDGGD IYHSVSQARP RFLLLGLLLL TVGVGIFLLP
  HCV12083
            ADADRLDLSS WFTVGAGGGD IYHSMSRARP RNLLLCLLLL SVGVGIFLLP
   HCV1480
            PAASQLDLSN WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
  HCVPOLYP
            PAAFQLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
      HD 1
   HPCCGAA
            TAAGRLDLSG WFTAGYSGGD IYHSVSHARP RWFWFCLLLL AAGVGIYLLP
     HPCFG PTAGQLDLSS WFTVGVGGND IYHSVSRART RHLLLCLLLL TVGVGIFLLP
HPCGENANTI PAASQLDLSK WFVAGYGGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
  HPCGENOM PAASRLDLSG WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
   HPCHUMR PAASRLDLSG WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
      HPCJ PAASQLDLSS WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGVYLLP
    HPCJCG PAASQLDLSG WFVAGYNGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
  HPCJK046
           RDAHRLDLSG WFVAGYSGGD IFHSVSHARP RVLLLCLLLL TVGVGIFFLP
            PQAGLLDLSR WFTVGAGGND IYHSVSRARS RHLLLGLLLL TVGVGIFLLP
  HPCJK049
           PAASQLDLSS WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
    HPCJTA
           PAASQLDLSS WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
    HPCJTB
    HPCK3A PAAGQLDLSS WFTVGVGGND IYHSVSRART RYLLLCLLLL TVGVGIFLLP
 HPCPLYPRE AAAGQLDLSG WFTAGYSGGD IYHSVSHARP RWIWFCLLLL AAGVGIYLLP
   HPCPOLP PEARLLDLSS WFTVGAGGGD IYHSVSRARP RLLLLGLLLL FVGVGLFLLP
     HPCPP PEASQLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
  HPCUNKCD PAASRLDLSG WFVAGYSGGD IYHSLSRARP RWFMLCLLLL SVGVGIYLLP
           PEASQLDLSG WFVAGYSGGD IYHSLSRARP RWFMWCLLLL SVGVGIYLLP
     MKC1A
           PEARLLDLSS WFTVGAGGGD IYHSVSRARP RLLLLSLLLL LVGVGLFLLP
     NDM59
           PAAGQLDLSS WFTVGVGGND IYHSVSRART RHLLLCLLLL TVGVGIFLLP
      NZLI
           ADADRLDLSS WFTVGAGGGD IYHSMSRARP RCILLCLLLL TVGVGIFLLP
      SA13
     Th580
           AAASQLDLSG WFVAGYDGGD IYHSVSRARP RLLLLGLLLL TVGVGIFLLP
           PRAGQLDLSI WFTVGVGGND IYHSVSRART RYLLLCLLLL TVGVGIFLLP
Type 3a CB
   TypeV D
           PATGQLDLSS WFTVGVGGND IYHSVSRART RYLLLCLLLL TVGVGIFLLP
     VN004
           RGASALDLSG WFTSGYGGGD VYHSASRARP RFLLLCLLLL SVGVGIFLLP
           RGAANLDLSG WFVSGGSGGD IFHSVSRARP RNLLLCLLLL TVGVGIFLLP
     VN235
          PDAARLDLSG WFISGFSGGD IYHSVSRARP RIFLLCLLLL SVGVGIFLLP
     VN405
           3051
    BEBE1
           AR
    D89815
           NR
ED43type 4
           AR
    HC_C2
           NR
    HC G9
           NR
 HCU16326
           NR
HCV H CMR
           NR
   HCV J1
           NR
 HCV J483
   HCV J8
           AR
  HCV JK1
```

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HCV_JS NR HCV_K1_R1 NR HCV_K1_R2 NR HCV_K1_R3 NR HCV_K1_S1 HCV_K1_S2 NR HCV_K1_S3 NR HCV_L2 NR HCV_N N. HCV12083 AR HCV1480 AR HCVPOLYP NR HD_1 NR **HPCCGAA** NR **HPCFG** AR HPCGENANTI NR HPCGENOM NR NR **HPCHUMR** HPCJ NR **HPCJCG** NR HPCJK046 PR HPCJK049 AR **HPCJTA** NR HPCJTB NR **НРСКЗА** AR HPCPLYPRE NR HPCPOLP AR HPCPP NR HPCUNKCD NR MKC1A NR NDM59 AR NZLI AR SA13 AR Th580 AR Type_3a_CB AR TypeV_D AR VN004 AR VN235 AR VN405 AR

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Table 23. HIV Fusion Construct

VPLQLPPLKAMTNNPPIPV

EP-HIY-1090 MGMQVQIQSLFLLLLWVPGSRGKLVGKLNWAGAAILKBPVHGVNAACPKV8FBPIKIPIHYCAPA KAKFVAAWILKAAAKAFPVRPQVPLGAAKLTPLCVTLGAAAVLABAMSQVKVYLAWVPAHKG AAAAIFQSSMTKKTTIFCABDAKNIPYNFQSQGVVKHPVHAGPLANVTVYYGVPVWKKAAAQMA vfiinfknaaayplaslrslfnltfgwcfkinriiQqllfinakiQnfrvyyrkaavtikiggqikk

ATGGGAATGCAGGTGCAGATCCAGAGCCTGTTTCTGCTCCTCCTGTGGGTGCCCGGATCCAGA GGAAAGCTGGTGGGCAAACTCAACTGGGCCGGAGCTGCAATCCTGAAGGAGCCCGTCCACGG ACCTGCCAAAGCTAAGTTTGTGGCCGCTTGGACCCTCAAGGCCGCTGCAAAAGCCTTCCCAGT GAGGCCCCAGOTGCCTCTGGGCGCCCCTAAACTCACACCACTGTGCGTCACTCTGGGAGCCGC GGGGGCCGCTGCAGCCATCTTTCAGTCTAGCATGACCAAGAAAACAACTCTGTTCTGTGCCTC CGACGCTAAGAACATCCCTTATAATCCACAGTCTCAGGGCGTGGTCAAGCATCCCGTGCACGC CGGACCTATTGCTAACGTGACCGTGTACTATGGGGTCCCAGTGTGGAAGAAGCCGCTGCACA GATGGCCGTGTTTATTCACAATTTCAAAAACGCCGCTGCATACCCCCTCGCCAGCCTGAGATC CCTCTTCAACCTGACATTCGGCTGGTGCTTTAAGCTGAACCGGATCCTGCAGCAACTGCTCTTT ATCAATGCTAAAATCCAGAACTTCCGCGTCTACTATAGGAAGGCTGCAGTGACTATCAAAATT GGCGGACAACTGAAGAAAGTGCCTCTCCAGCTGCCCCTCTCAAGGCAATGACCAACAATCC CCCTATCCCAGTCTGA

Table 24. HBV GCR-3697 Fusion Construct

GCR-3697	Polynucleotide
SEQ ID	
NO:	1 Start
	TIGGECATGCAGGTGCAGATCCAGAGCCTGTTCCTGCTCCTGCTGTGGGTGCCAGGAAGCAGAGGCTTTCTC TGTCCCTGGGCATCCACCTGAACGCCGCTGCAAAGTACACCAGCTTCCCTGGCTGCTCAACGCCGCTGCC CGGTTCAGCTGGGCTGTCCCTGTGCCCTTCAACGCAGCCTTCCCCCACTGCCTGC
GCR-3697	Polypeptide
SEQ ID NO:	I † MGMQVQIQSLFLLLLWVPGSRGFLLSLGIHLNAAAKYTSFPWLLNAAARFSWLSLLVPFNAAFPHCLAFSYMKA ALVVDFSQFSRGAILLLCLIFLLNAAAHTLWKAGILYKKAWMMWYWGPSLYKAYPALMPLYACIGAAAWLSLL VPFVNAAAGFLLTRII TINAAAIPIPSSWAEKAA A FEW LYGGCWAWNAYWGPSLYKAYPALMPLYACIGAAAWLSLL
	VPFVNAAAGFLLTRILTINAAAIPIPSSWAFKAAAEYLVSFGVWNLPSDFFPSVKAAAFLPSDFFPSVKAAADLLD TASALYNSWPKFAVPNLKAAASAICSVVRRKLSLDVSAAFVNAAKFVAAWTLKAAAKAANVSIPWTHKGAA GLSRYVARLNAAASTLPETTVVRRKIIPAAMPHLLKAAARWMCLRRFIINASFCGSPYKAAYMDDVVLGVNAL WFHISCLTFKAAATPARVTGGVFKAAALTFGRETVLEYKQAFTFSPTYKNAGTSFVYVPSALNPADGPGPGLCQ VFADATPTGWGLGPGPGRHYLHTLWKAGII.YKGPGPGPHHTALRQAILCWGELMTLAGPGPGESRLVVDFSQFS RGNGPGPGFPLLAQFTSAICSVVGPGPGLVPFVQWFVGLSPTVGPGPGLHLYSHPIILGFRKIGPGPGSSNLSWLSL DVSAAFGPGPGLQSLTNLLSSNLSWLGPGPGAGFFLLTRILTIPQSGPGPGVSFGVWIRTPPAYRPPNAPIGPGPGV GPLTVNEKRRLKLIGPGPGKQCFRKLPVNRPIDWGPGPGAANWILRGTSFVYVPGPGPGKQAFTFSPTYKAFLCG

Table 25. HBV AOSIb2 Fusion Construct

Polynucleotide 1 Start
1 Start
↑ ATGGAATGCAGGTGCAGATCCAGAGCCTGTTTCTGCTCCTCTGTGGGTGCCCGGGTCCAGAGGACACAC CCTGTGGAAGGCCGGAATCCTGTATAAGGCCAAGTTCGTGGCTGCCTGGACCCTGAAGGCTGCCGCTTTCCT GCCTAGCGATTTCTTTCCTAGCGTGAACTTCCTGCTGGCTG
Polypeptide
OF OF THE COLUMN
I † MGMQVQIQSLFLLLLWVPGSRGHTLWKAGILYKAKFVAAWTLKAAAFLPSDFFPSVNFLLSLGIHLYMDDVVL GVGLSRYVARLFLLTRILTISTLPETTVVRRQAFTFSPTYKGAAAWLSLLVPFVNIPIPSSWAFKTPARVTGGVFKV GNFTGLYNLPSDFFPSVKTLWKAGILYKNVSIPWTHKGAALVVDFSQFSRNSAICSVVRRALMPLYACI \$\delta_{\text{L}} \text{L}\$
_

Table 26. HCV Fusion Construct

HCYAJII(IP)
MGMQVQIQSLFLLLLWYPGSRGRLGVRATRKKAAAKTERRSQPRNLPGCSFSIFNDLMGYIPLVK
YLLPRRGPRLNTLCGFADLMGYRMYVGGVEHRKLLFNILGGWVKAAALADGGCSGGAYRLIVFP
DLGVKFWAKHMWNFIGVAGALVAFKKQLFTFSPRRNGYLVAYQATVAAALLFLLLADALIFCHS
KKKYLVTRHADVLGFGAYMSKCTCGSSDLYHMWNFISGIFWAKHMWNFKKAAAVLVGGVLAA

AFLLLADARVL8AFSLHSYILAOYGAGVWMNRLIAFANAAAKFVAAWTLKAAA*

GAATTCGCCGCCACCATGGGAATGCAGGTGCAGATCCAAAGCCTGTTTCTGCTCCTCTGTGG OTGCCCGGCTCCAGAGAAGAAGCTGGGCGTGAGAAGAAGAAGAAGAAGAAGACTGCCGCTAAAAC AAGOGAGOGCTOOCAGOCCAGGAACCTGCCTGGATGCTCTTTCAGCATCTTTAATGACCTCAT GGGGTACATTCCACTGGTGAAGTATCTGCTCCCCAQACGGGGCCCTCGCCTGAACACTCTCTG TOGATTTGCTGATCTGATGGGGTACAGGATGTATGTCGGCGGAGTCGAACACAGAAAACTGCT CTTCAACATCCTGGGCGGATGGGTGAAGGCTGCCGGCTCTGGCCGACGGGGGATGCAGCGGCG GAGCITACAGGCICATTOTCTTTCCCGATCTCGGAGTCAAATTTTGGGCAAAGCACATGTGGA ATTTCATCGGGGTGGCCGGAGCCCTGGTCGCTTTTAAAAAGCAGCTCTTCACCTTCTCCCCAA GACGGAACGGATACCTCGTCGCCTACCAGGCCACTGTGGCTGCAGCTCTGCTCCTGCTCCC TGGCCGATGCACCATCTTCTGCCATTCCAAGAAAAGTATCTGGTCACCAGACATGCTGACG TGCTGGGGTTTGGCGCCTACATGAGCAAGTGCACCTGTGGCAGCTCCGACCTGTATCACATGT GGAACTTTATTTCTGGAATCTTTTGGGCCAAGCACATGTGGAATTTTAAGAAAGCCGCTGCAG TCCTGGTGGCGGCGTCCTGGCAGCCGCTTTCCTGCTCCTGGCAGACGCCAGGGTGCTGTCTG OCTTCAGCCTOCACTOCTACATOCTCGCAGGGTATGGCGCAGGCGTGTGGATGAATCGGCTGA TCGCCTTTGCCAATGCTGCAGCTAAATTCGTGGCAGCCTGGACACTGAAAGCAGCTGCATGAG GATCC

Table 27. Plasmodium falciparum Fusion Construct

MGMQVQIQSLFLLLLWVFGSRGFMKAVCVBVNVTCONGIQVRKGLIMVLSFLNAALFHIFDGDN BIKAALLACAGLAYKKSFLFVBALFNAAPSDGKCNLYKAAQTNFKSLLRNLPSHNERGYKAAGVS ENIFLKNAAAYFILVNLLIKAAAILSVSSFLFVNTPYAGEPAPFKAAAKYKLATSVLKAAVFLIFFDL FLNYYIPHQSSLKAAGLLGNVSTVGAVLLGGVGLVLNLACAGLAYKKAKFIKSLFHIFKAAFYFIL VNLLKAFLIFFDLFLVKALFFIIFNKNYYGKQENWYSLKFVBALFQBYNAAAKFVAAWTLKAAAK ILSVFFLANAVLAGLLGNVNFQDEENIGIYKAAALYISFYFIKAFILVNLLIFHNAALPYGRTNLKAA HVLSHNSYEKNAAAKYLVIVFLI

GCCGCCACCATGGGAATGCAGGTGCAGATCCAGAGCCTGTTTCTGCTCCTCCTGTGGGTGCCC GGATCCAGAGGATTTATGAAAGCTGTCTGTGTGAGAGGTGAATGTAACATGCGGTAACGGAAT TCAGGTGAGAAAGGGACTCATCATGGTACTCAGCTTTCTGAACGCAGCCTGTTCCACATCTT TGACGGAGACAATGAAATCAAAGCCGCATTGCTCGCCTGTGCCGGACTAGCCTATAAAAAGA GTTTOCTTTCGTTGAAGCACTATTTAACGCAGCACCCAGTGACGGTAAATGCAACCTATATA AAGCAGCTCAGACTAATTTCAAAAGCCTGTTAAGAAATCTGCCCTCAGAGAATGAAAGGGGT TACAAAGCCGCCGGCGTGTCCGAGAATATTTTCCTGAAGAACGCCGCTGCTTATTTTATACTC GTGAATCTACTCATAAAGGCAGCOGCAATCCTTTCAGTGTCCAGCTTTCTGTTTGTTAACACAC CATATGOGGGGGGGGGGCTCCTTTCAAGGCTGCAGCAAAATACAAGCTTGCCACATCAGTAT TGAAAGCAGCTGTGTTTTGATATTCTTTGATCTTTTTTTAAACTACTACATACCTCATCAGTCT AGTCTTAAAGCAGCCGGGCTACTGGGGGAACGTCTCTACTGGGGGGCCGTCTTACTTGGAGGA GTTGGCCTCGTGTTGAACCTCGCGTGCGCAGGTCTGGCCTACAAAAAGCGAAATTCATCAAG TCTCTGTTCCACATTTTTAAAGCCGCATTCTATTTCATACTAGTGAACCTTCTCAAAGCTTTCCT GATCITCTTCGATCTATTCCTCGTAAAAGCGCTATTCTTCATTATCTTTAACAAAAATTATTAC GGCAAGCAAGAAATTGGTACTCACTCAAGTTTGTAGAAGCTCTGTTCCAGGAATACAACGCC GCTGCTAAATTCGTTGCAGCTTGGACCCTGAAAGCAGCTGCAAAGATCCTATCGGTCTTCTTTC TOGCTAATGCCGTATTAGCAGGACTTCTAGGCAACGTGAACTTTCAAGACGAAGAGAATATAG GCATCTACAAAGCCGCAGCACTGTACATTCATTCTACTTCATCAAGGCCTTCATACTGGTCAA CCTTCTGATATTTCATAATGCAGCACTGCCATATGGGAGACCAACTTGAAAGCGGCCCACGT OTTGAGOCACAACTCCTACGAGAAGAACGCCGCCGCGAAATATCTCGTCATTGTCTTCCTGAT TTGA ...

Table 28. Mycobacterium tuberculosis Fusion Construct

TE.1 MQVQIQSLFLLLLWVPGSRGRMSRVTIFTVKALVLIMLPVVNLMIGTAAAVVKALVLLMLPVGA GIMTAVYLVGAAAMALLRLPVKRMFAANLGVNSLYFGGICVGRLPLVIPAVNAAAAKPVAAWT LKAAAKAAARLMIGTAAAGFVVALIPLVNAMTYAAPLFVGAAAAMALIRIPLV

ATGCAGOTGCAGATCCAGAGCCTGTTTCTGCTCCTCTGTGGTGCCCGGATCCAGAGGAAGG
ATGAGCAGAGTGACCACATTCACTGTCAAGGCCTGGTGCTCCTGATGCTCCCCGTCGTGAAC
CTGATGATCGGCACCGTGCAGCCGTCGTQAAAGCTCTCGTCCTGCTGCTCCTGTGGGA
GCAGGGCTGATGACAGCCGTGTACCTGGTCGGGGCTGCAGCCATGGCCCTCCTGCGGCTGCCA
GTQAAGCGCATGTTTGCTGCAAATCTGGGAGTCAACTCCCTCTATTTCGGGGGCATTTGCGTG
GGAAGGCTGCCCTCGTGCTGCTGCTGAATGCCGCTGCCAAATTTGTCGCCGCTTTGG
ACTCTGAAGGCAGCCGCTAAGGCCGCTGCAAAGACTGATGATCGGGACCGCCGCTGCCGGCTT
CGTGGTCGCCCTGATTCCCCTGGTGAACGCCATGACATACGCAGCTCCTCTTTTTTGTGGGAGC
CGCTGCAGCCATGGCTCTCCTGCGGCTGCCACTTGGTTGTG

Table 29. Hepatitis B Virus Core Protein (SEQ ID NO: _)

MQLFHLCLIISCSCPTVQASKLCLGWLWGMDIDPYKEFGATVELLSFLPSDFFPSVRD LLDTASALYREALESPEHCSPHHTALRQAILCWGELMTLATWVGVNLEDPASRDLVV SYVNTNMGLKFRQLLWFHISCLTFGRETVIEYLVSFGVWIRTPPAYRPPNAPILSTLPE TTVVRRRGRSPRRRTPSPRRRRSQSPRRRRSQSRESQC

WHAT IS CLAIMED IS:

- A method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, variants of a peptide epitope 8-11 amino acids in length, each variant comprising primary anchor residues of the same HLA class I binding motif; and
 - b) determining whether one of said variants comprises only conserved nonanchor residues in comparison to at least one remaining variant, thereby identifying a candidate peptide epitope.
- A method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, variants of a
 peptide epitope 8-11 amino acids in length, each variant comprising primary
 anchor residues of the same HLA class I binding motif;
 - b) determining whether each of said variants comprises conserved, semiconserved or non-conserved non-anchor residues in comparison to each of the remaining variants; and
 - c) identifying a variant which comprises only conserved non-anchor residues in comparison to at least one remaining variant.
- A method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, a population of variants of a peptide epitope 8-11 amino acids in length, each peptide epitope comprising primary anchor residues of the same HLA class I binding motif;
 - b) choosing a variant selected from the group consisting of:
 - a variant which comprises preferred primary anchor residues of said motif; and
 - ii) a variant which occurs with high frequency within the population of variants; and

- c) determining whether the variant of (b) comprises only conserved nonanchor residues in comparison to at least one remaining variant, thereby identifying a candidate peptide epitope.
- A method for identifying a candidate peptide epitope which induces a HLA class I CTL response against variants of said peptide epitope, comprising
 - a) identifying, from a particular antigen of an infectious agent, a population of variants of a peptide epitope 8-11 amino acids in length, each peptide epitope comprising primary anchor residues of the same HLA class I binding motif;
 - b) choosing a variant selected from the group consisting of:
 - a variant which comprises preferred primary anchor residues of said motif; and
 - a variant which occurs with high frequency within the population of variants; and
 - c) determining whether the variant of (b) comprises conserved, semi-conserved or non-conserved non-anchor residues in comparison to each of the remaining variants; and
 - d) identifying a variant which comprises only conserved non-anchor residues in comparison to at least one remaining variant.
- 5. The method of claim 1, wherein (b) comprises identifying a variant which comprises only conserved non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- 6. The method of claim 2 or 3, wherein (c) comprises identifying a variant which comprises only conservative non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.
- 7. The method of claim 4, wherein (d) comprises identifying a variant which comprises only conservative non-anchor residues in comparison to at least 25%, at least 50%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% of the remaining variants.

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- 8. The method of any of claims 1-4, wherein (a) comprises aligning the sequences of said antigens.
- 9. The method of claim 3 or 4, wherein (b) comprises comprises choosing a variant which comprises preferred primary anchor residues of said motif.
- 10. The method of claim 3 or 4, wherein (b) comprises comprises choosing a variant which occurs with high frequency within said population.
- 11. The method of claim 10, wherein (b) comprises ranking said variants by frequency of occurrence within said population.
- 12. The method of claim 3 or 4 wherein (b) comprises choosing a variant which comprises preferred primary anchor residues of said motif and which occurs with high frequency within said population.
- 13. The method of claim 12, wherein (b) comprises ranking said variants by frequency of occurrence within said population.
- 14. The method of any of claims 1-13, wherein the identified variant comprises the fewest conserved anchor residues in comparison to each of the remaining variants.
- 15. The method of any of claims 1-4, wherein the remaining variants comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 27, 28, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 280, or 300 variants.
- 16. The method of any of claims 1-15, wherein the infectious agent is selected from the group consisting of: HIV, HBV, HCV, HPV, Plasmodium falciparum, Influenza virus, and Dengue virus, Epstein-Barr virus, Mycobacterium tuberculosis, Chlamydia, Candida albicans, Cryptococcus neoformans, Coccidoides spp., Histoplasma spp., Aspergillus fumigatis, Plasmodium spp., Trypanosoma spp., Schistosoma spp., and Leishmania spp.
- 17. The method of claim 16, wherein the infectious agent is selected from the group consisting of: HIV, HBV, HCV, HPV, *Plasmodium falciparum*, Influenza virus, and Dengue virus.
- 18. The method of claim 16, wherein the infectious agent is HIV and the antigen is selected from the group consisting of: Gag, Env, Pol, Nef, Rev, Tat, Vif, Vpr, and Vpu.

- 19. The method of claim 16, wherein the infectious agent is HBV and the antigen is selected from the group consisting of: Pol, Env, Core, and NS1/Env2.
- 20. The method of claim 16, wherein the infectious agent is HCV and the antigen is selected from the group consisting of: Core, E1, E2, NS1, NS2, NS3, NS4, and NS5.
- 21. The method of claim 16, wherein the infectious agent is HPV and the antigen is selected from the group consisting of: E1, E2, E3, E4, E5, E6, E7, L1, and L2.
- 22. The method of claim 16, wherein the infectious agent is *Plasmodium falciparum* and the antigen is selected from the group consisting of: CSP, SSP2, EXP1, LSA1.
- 23. The method of any claims 1-4, wherein the selected variant and the at least one remaining variant comprise different primary anchor residues of the same motif or supermotif.
- 24. The method of any of claims 1-4, wherein the motif or supermotif is selected from the group consisting of those in Tables 1-2.
- 25. The method of any of claims 1-4, wherein the conserved non-anchor residues are at any of positions 3-7 of said variant.
- 26. The method of any of claims 1-4, wherein the variant comprises only 1-3 conserved non-anchor residues compared to at least one remaining variant.
- 27. The method of any of claims 26, wherein the variant comprises only 1-2 conserved non-anchor residues compared to at least one remaining variant.
- 28. The method of any of claims 27, wherein the variant comprises only 1 conserved non-anchor residue compared to at least one remaining variant.
- 29. The method of claim 16, wherein the infectious agent is HPV, and further wherein, the HPV infectious agent is selected from the group consisting of HPV strains 16, 18, 31, 33, 45, 52, 56, and 58.
- 30. The method of any of claims 1-29, wherein the variants are a population of naturally occurring variants.

METHODS OF IDENTIFYING OPTIMAL VARIANTS OF PEPTIDE EPITOPES ABSTRACT OF THE DISCLOSURE

The present invention is directed to methods for selecting a variant of a peptide epitope which induces a CTL response against another variant(s) of the peptide epitope, by determining whether the variant comprises only conserved residues, as defined herein, at non-anchor positions in comparison to the other variant(s). The present invention is also directed to variants identified by the methods above; peptides comprising such variants; nucleic acids encoding such variants and peptides; cells comprising such variants, and/or peptides, and/or nucleic acids; compositions comprising such variants, and/or peptides, and/or nucleic acids, and/or cells; as well as therapcutic and diagnostic methods for using such variants, peptides, nucleic acids, cells, and compositions.

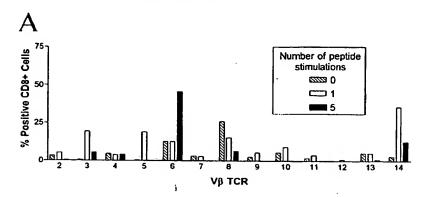
FIGS. 1A-1C

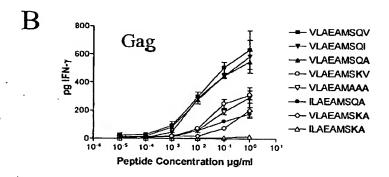
	_		Binding	# 15	solate	s	Immunogenicity (SU)
		Amino Acid Sequence		Total	В	С	10 100 1000 10000
٨	P	KLTPLCVTL	77.0	134	19	55	
A	A	KITPLCVTL	461.2	2			
		KMTPLCVTL	44.7	1		1	Bearing and the Control
		KLTPLCVTM	340.3	1			
	NA	RLTPLCVTL	27.6	3		3	=n =01_C1025
		QLTPLCVTL	63.6	5	1		
		ELTPLCVTL	7190	3	1		₽
		KLTFLCVTL	19.4	1			the commence of the section of the section of
		KLTSLCVTL	91.0	1		1	
		K L T Q L C V T L K L T P F C V T L	23.8	1		1	
			87.3	1			i
			597.0	1			
			1.7	1			
		K L T P L C V P L K L T P L C V S L	14.6 67.2		1		
		KLTPLCVAL	208.6	1			the second of a second second
		KLTPLCVIL	356.2	3 1			
	М	QITPLCVTL	975.9	-			
		QMTFLCVQM	3153	3			
		KMTFLCVQM	1793	1			,
		,		•			•
							10 100 1000 10000
_	Ρ	VLAEAMSQV	49.9	54.	15	3	
В	A	VLAEAMSQA	23.8	67	1	36	
		VLAEAMSQT	289.6	11	•	9	
		VLAEAMSQI	70.9	1	1	•	
	NA	ILAEAMSQV	38.0	5	3		
		VLAEAMGQV	55.3	1	-	1	
		VLAEAMSRV	39.8	1	1	•	CONTRACTOR CO.
		VLAEAMSKV	230.5	1		1	
		VLAEAMSHV	29.3	2			020-02000 2000
	М	ALAEAMSQA	15.0	1		1	
		ILAEAMSQA	29.3	3		2	
		V L G E A M S Q A	176.0	1		1	H
		VLAEAMSKA	69.4	1		1	
		VLAEAMSRA	127.4	1			
		VLAEAMSHA	148.8	6		4	
		VLAEAMSHT	243.5	1		1	
		VLAEAMSAA	23.9	1			2011 10 10 10 10 10 10 10 10 10 10 10 10
		VLAEAMATA	6.7	1			120 Cara (C.)
		VLAEAMAAA	17.2	1			Mary and a series and the
		ILAEAMSKA	72.4	1		1	
		ILAEAMASA	22.2	1			
							10 100 1000 10000
~	-		~~ -				
\mathbf{C}	<u>P</u>	RILQQLLFI	72.5	86	15	28	
_	А	RLLQQLLFI	27.0	2	_	1	
		RTLQQLLFI	151.6	10	2	4	
		R M L Q Q L L F I R V L Q Q L L F I	14.7	4	1	3	
			27.1	3		3	
			27.7	21		2	
			1427	6		2	Hillian Control of the land
	NA		122.9				
	14/	KILQQLLF! T!LQQLLF!	40.5	2		1	
		RILOQMLFI	94.6	1			
		RILQQPLFI	186.7 140.1	1		1	
		RILOGLLLI	199.2	1	1	•	
	М	RVLQQLLFV	10.2	'		1	
	•	RMLQQLLFV	21.5			•	
		RMLQQLLFT	21.5 125.7	2			
		RTLQQLLFA	948.4	1	1	1	
		RTLQQLLFT	948.4 9708		,		
		RTLQQLLFV	120.4	1 10		1	
		RTLQQLMFI	143.1	10		1	
		RMLQHLLFI	15.7	1		1	B-4
		RILQHLLFA	160.3	i		•	
		RILORLLEV	64.0	i		1	
		RTLQLLLFV	4.7	1		•	

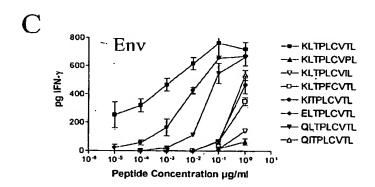
FIGS. 1D-1E

		Binding	44.0				
-	Amino Acid Sequence			solate		Immunogenicity (SU)	
D		IC50 (nM)	Tota		<u>c</u>	10 100 1000	10000
I)		15.5	18	13	1		
_	AVAIKIGGQLK	151.3	2	1		BEB-4	
	VTIKIGGQLR	64,0	2			L ಎ. ಸುದ್ದಾರ್ಯದಲ್ಲಿ ಎ. ಆ. ಪ್ರ	
	NAVTVKIGGQLK	60.7	11	1			
	VTIRIGGQLK	14.4	3	2		Constitution of the second	
	VTIKVGGQLK	59.4	2	2		e se se innesse annual	
	VTIKIEGQLK	69.4	2	1		(MACAGE) 4	
	VTIKIGGQIK	183.5	1				
	2NA V T V K I G G Q L R	194.1	3				
	VTVKIGGELK	39.2	1				
	VTVKIEGQLK	23.2	4			SERVICE AND THE PARTY OF THE PA	
	VTVKVGGQLK	54.3	3			The same about the	
	VTVRIGGQLK	15.2	6			ear Tearmanair III	
	VTIRIGGQLR	22.9	2				
	VTIRVGGQLK	13.2	1				
	VAIKIGGQIK	940.2		1		Γ'	
	VNIKVGGQLK	1768	i	-	4		
	VTIKIGGOIR	388.5	1		1		
	3NA V T I K L G G Q I R	219.5	- -				
	VTVKIEGQLR	143.0	-			C	
	VTVKVGGQLR	198.7	4			DESCRIPTION S	
	VTIRVGGQLR		2				
	VSIKVGGQIK	17.3	1				
		85.9	30	3	30		
	4NA V T I R V A G Q V K	19.3	1_			<u> </u>	
		20.B	1			L · · ·	
	VSIRVGGOTK	20.9	1			P	
	VSIRVGGQIK	90.6	4		4		
	VSIKVGGQIR	1339	6	- 1	6		
	VTVRIGGMQK	13.4	1			•	
	VSIRVGGQTR	240.6	1	•	1		
	ITVKIGKEVR	12904	1			1	
_	_ 1					1D 100 1000	10000
E	PVTVYYGVPVWK		99	21 3	30		_
_	AVTVYYGVPVWR		40	. 1	8		_
	NAVTIYYGVPVWK		1				
	V T V Y D G V P V W K		1		1	In the second se	
	VTVYYGVPIWK	2.3	2				
	MITVYYGVPVWR	75.9	1				
	V T I Y Y G V P V W R	3.0	1				
	V T V Y D G V P V W R	245.7	1	1		700	
	VTVYYGIPVWR	16.7	1				
	<u>VTVYYGVPVR</u> R	270.7	1			-	

FIGS. 2A-2C







FIGS. 3A-3B

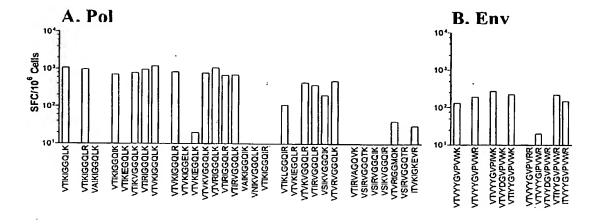


FIG. 4

	Binding	Predicted Cr	oss-reactivity	Immunogenicity (SU)
Amino Add Sequence	IC ₅₀ (nM) # Isolates	MTNNPPIPV	MTSNPPIPV	10 100 1000 10000
MTSNPPIPV	52.8 60	-	+	
MTNNPPIPV	128.4 33	+	+	
MTSNPPVPV	21.8 26	_	+	
MTGNPPIPV	125.1 15	-	. +	
MTGNPPVPV	2021 9	-	+	
MTNNPPVPV	85.6 6	+	+	
MTANPP.VPV	20.0 3		+	
MTHNPPIPV	167.0 2	+	-	
MTANPPIPV.	2.3 1	-	+	
MTSDPPIPV	107.4 1	-	+	н
MTGNPSIPV	15.8 1	-	+	H
MTGNPAIPV	1200 1	٠ _	+	■ MTNNPPIPV
MTSNPAIPV	1465 1	-	+	OMTSNPPIPV
MTRNPPVPV	9171 1	-	-	

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